The Neural Basis of Psychotic-Like Experiences

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The Neural Basis of Psychotic-Like Experiences

Thesis for the Research Degree of Doctor of Philosophy in Psychosis Studies

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For my dear wife, Eleni

and my parents, Irene and Giorgos

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Background

Despite ongoing research in the field of psychosis, its aetiology remains an enigma. Psychosis proved to be a convoluted brain disorder and lack of a biological understanding has had a negative impact on the development of efficient treatments, which further undermined the health and well-being of sufferers.

Contemporary models of psychosis have enriched the long-standing ***dopamine hypothesis*** (*subcortical pre-synaptic hyperdopaminergia* with *prefrontal hypodopaminergia*) with the addition of the ***aberrant salience hypothesis***: context-independent firing of dopamine neurons, produces an aberrant sense of novelty and salience to irrelevant stimuli. This can give rise to development of hallucinations, and delusions, as cognitive explanations to account for abnormal experiences. The aberrant salience model has thus placed ***"top-down" cognitive control mechanisms*** at the core of the aetiology of psychosis and has reinforced the use of various cognitive tasks, alone or in combination with functional neuroimaging, as paradigms for the study of psychotic phenomenology. Among the several tasks employed, ***reward-based tasks*** were often selected to explore aberrant salience and more socially-relevant processes of psychosis, while ***face perception tasks*** were chosen to assess cognitive control and emotionally-relevant processes of psychosis.

Another persistent idea in psychosis studies has been the ***developmental model***, which postulates that psychosis emerges as the lengthy outcome of multiple insults to normal brain development, dating from in utero life, through childhood to adolescence; this morbid process is further perplexed by the interplay of genetics and the environment. Due to the complex nature of these pathogenic interactions, various degrees of symptomatology can be observed, ranging from subtle prodromal manifestations, to fully blown clinical presentations. This was conceptualised in the prevalent notion of the ***psychosis continuum*** or the ***extended psychosis phenotype***: psychotic symptoms are not "all-or-nothing" phenomena but form a spectrum with normal experiences. The natural history of these symptoms was typically described as starting with a transitory state (***psychosis proneness***) which later becomes abnormally persistent and finally clinically significant. This is how the concept of ***ultra-high-risk for psychosis*** or the ***at-risk-mental-state*** emerged: individuals with sub-clinical psychotic manifestations, called ***psychotic-like-experiences*** or ***attenuated psychotic symptoms***, carry an increased risk for future transition to psychosis. The model was supported by a wealth of epidemiological and neuroimaging data, such the presence of dysconnectivity between various brain areas across the whole psychosis spectrum; further use of functional neuroimaging was consequently seen as the royal road to discover ***brain biomarkers*** as predictors of psychosis. A notable consequence of the psychosis continuum model, is that the study of psychosis should

no longer be restricted to clinical populations; healthy people at high risk for psychosis could also offer a useful test of this new paradigm in more accessible and more widely available samples.

I was fortunate in gaining access to a large cohort of adolescents from the ***IMAGEN*** project, part of an existing longitudinal study, combining *neuroimaging data during a face perception and a reward-based task*, *selected measures from CANTAB neurocognitive battery* with *measures of psychotic-like experiences*, and observing my subjects during early and late adolescence. My aim was to investigate the neural correlates of this prodromal [*] psychotic presentations beyond the bounds of the illness phenotype, the use of antipsychotic medication, and test the continuum models of psychosis.

I spent 6 years in total, working on this project part-time, between July 2012 and July 2018. The momentum was quite right when I joined the IMAGEN team, as their second follow-up (at age 19, our FU data) was about to begin, and the introduction of CAPE-42 (our basic tool for the measurement of psychotic-like experiences) to the battery of assessments come just at the right time.

The initial phase of my studies, ***years 2012-2014***, was spent in familiarising with the extend of IMAGEN database; obtaining a fund of £10,000.00 to support the introduction of CAPE-42; learning to apply neuroimaging analysis by attending SPM courses; practising neuroimaging analysis and the use of MATLAB scripts in limited data sets from age 14 and some preliminary CAPE data; refining the design of the studies; drafting initial versions of introductory chapters (biomarkers of psychosis, psychotic-like experiences, CAPE questionnaire, cognitive tasks in schizophrenia) by conducting extended literature reviews.

Data from our FU endpoint started becoming available from ***year 2015*** and a new IMAGEN database become available, providing data with enhanced quality. I spent this year in compiling all anonymised data that were used in my main analysis. Customised spreadsheets with behavioural and neurocognitive data were prepared, while neuroimaging data were stored in KCL servers, to allow safe storage and back-up and fast analysis via remote access.

Yeas 2016 was spent in conducting the main bulk of neuroimaging and consecutive factorial and exploratory analysis. Writing of study methodology and results was conducted during ***year 2017***. Finally, the drafting of the thesis, plus the preparation and submission of related articles

[*] The term “prodromal” is used in the thesis interchangeably with sub-clinical to indicate either subtle forms of symptoms and/or *a potential of* transition to more clinically significant manifestations; thus its use is different the strict medical meaning of indication future transition to the next phase of the disease.

to high-impact factor journals was carried over in ***year 2018***, with publication process being ongoing at the time of submission, in May 2018. By the time of my oral examination, in July 2018 one article describing findings from the reward task, was already accepted for publication in JAMA Psychiatry.

Overview of the Thesis

In Chapter I, a selective review of the literature on key predictors of psychosis is provided, considering that the hunt for early biological markers of psychosis has been a major driving force for the present research. I list a representative selection of the many clinical, epidemiological, cognitive, genetic and neuroimaging studies which illustrate the complexity of the psychosis phenotype.

Chapter II, consists of two parts. In the first one, I review the literature on Psychotic-Like Experiences (PLE), the paradigm which was employed as a proxy for the sub-clinical manifestations of the psychotic phenotype. I examine the clinical, epidemiological and neuroimaging findings in individuals with this phenotype, and also the relationship of PLE with other aspects of the psychosis continuum. In the second part, I present the literature on the CAPE-42 questionnaire, the screening tool for PLE in the general population which was used in my studies; validation and cut-off levels for transition to psychosis are discussed, along with results from well-known longitudinal cohorts which employed this tool.

In Chapter III, I describe the face (FT) and reward (MID) tasks that were used in conjunction with functional neuroimaging in my studies and I summarize the wealth of fMRI data on those two tasks found in the literature of schizophrenia populations. As my study sample encompasses adolescents, I also provide a summary of neuroimaging data on the developing adolescent brain and some aberrant patterns observed in schizophrenia during this critical neurodevelopmental phase.

In Chapter IV, I describe the methodology of my studies, including my hypotheses, participants, material and analytical methods.

In Chapter V and Chapter VI, I present the results of the FT and MID neuroimaging studies respectively and the associated neurocognitive results; I also discuss the interpretation of those results, under the light of the relevant literature and contemporary models of psychosis.

Finally, in Chapter VII, the main results of both studies are reviewed in order to provide a succinct summary and I propose a programme of work that could usefully move the field forward.

Abstract

Objective

Psychotic-Like Experiences (PLE) are subclinical manifestation of psychotic symptoms and may reflect an increased vulnerability to psychotic disorders. Contemporary models of psychosis propose that dysfunctional reward processing and emotional dysregulation is involved in the aetiology of psychosis.

Objective

To examine the neuroimaging profile of healthy adolescents with an increased presence of PLE, during a face processing and a reward processing task.

Method

1,434 adolescents were assessed at two timepoints using functional MRI during a Faces Task (FT) and a Monetary Incentive Delay (MID) Task at age 14 and 19 years. The sample was stratified into two groups of high PLE and low PLE based on their scores on the CAPE-42 questionnaire at age 19. The first level analysis focused on a pre-defined contrast of [Angry Faces] – [Control Stimuli] for the FT and two pre-defined contrasts of [Anticipation of Large Win] – [Anticipation of No Win] and [Feedback of Large Win] – [Feedback of No Win] for the MID task. The second level analysis examined between-group differences using an a priori defined region of interest approach (ROIs). I performed a factorial analysis to examine the main effects of *group*, *time* and their interaction on brain activation. Additionally, I performed an exploratory analysis, by employing both a cross-sectional design to compare brain activation levels between the high PLE and low PLE groups at ages 14 and 19, and a longitudinal design to compare brain activation levels between the two timepoints.

Results

FT: Adolescents presenting with elevated overall PLE scores at age 19 years exhibited an early state (BL) of hyperactivation in right insular cortical areas, during perception of angry faces; this was replaced by a later state (FU) of hypoactivation in right prefrontal and right limbic cortical areas and left striatal subcortical areas, during perception of angry faces. There was a decrease in activation of right limbic cortical areas, from BL to FU, in the high general PLE group.

MID: Adolescents presenting with elevated overall PLE scores at age 19 years exhibited an early state (BL) of hypoactivation in left and right prefrontal and left limbic cortical areas, during reward feedback; this was replaced by a later state (FU) of hypoactivation in right

striatal subcortical areas, during the reward anticipation. There was also an increase in activation of left and right prefrontal areas, from BL to FU, in the high general PLE group.

Conclusions

The FT results suggest evidence of *aberrant changes* during adolescent development with reduced limbic and insular activation over time; this might reflect an under-recruitment of critical areas during perception of emotional faces.

The MID task results suggest evidence of *compensatory changes* during adolescent development with increased prefrontal activation over time; this might allow cognitive control mechanisms to contextualise the PLE, so to prevent transition to clinically significant symptoms; an observation which is consistent with the *aberrant salience model of psychosis*.

My findings reinforce the role of prefrontal, limbic and striatal brain areas in the aetiology of psychosis, beyond the bounds of the illness phenotype and without the confounds of the impact of the illness or the use of antipsychotic medication.

Chapter I: Biomarkers as Predictors of Psychosis

1.1. Introduction

Mental disorders in Europe are present in 38% of the population contributing to 26% of health burden and being a major cause of disability [1]. It is widely recognised that the increase in chronicity of mental illness is directly linked to poorer outcomes, which is broadly explained by neurodegenerative brain changes [2]. Both in affective [3] and psychotic [4] disorders, a longer duration of untreated illness is associated with poorer response or treatment-resistance. The idea that early intervention in psychiatric disorders can delay or even prevent transition to a clinical syndrome was first introduced in the field of psychosis [5] and is an important feature in the contemporary management of mental illness. Early intervention is based on the premise of identifying populations who are at high-risk of developing mental disorders, based on their epidemiological, clinical or biological characteristics. The concept of the at-risk-mental-state (ARMS), has evolved in psychosis to describe people with early prodromal symptoms who may later develop a clinical psychotic disorder [6]. Transitory developmental expression of psychosis *(psychosis proneness)* may become abnormally persistent *(persistence)* and subsequently clinically relevant *(impairment)*, depending on the degree of environmental risk the person is additionally exposed to [7†]. Tools using dimensionally scored symptoms, such as the Comprehensive Assessment of At-Risk Mental States (CAARMS) have been developed to allow for a better detection of those potentially vulnerable individuals [8]. It is crucial to identify key biological markers of elevated risk in order to optimise prediction.

Despite recent advances in the field of neuroimaging and genetics, and a wealth of relevant research with regards to psychiatric disorders, including psychosis, there has been very limited application to routine psychiatric practice to inform diagnosis and clinical decisions. The lack of a clear mechanism underpinning the pathophysiology of psychiatric disorders, and the use of a categorical nosology have been mooted as the key factors in hindering the identification of biomarkers in clinical use [9].

1.2. Clinical and Epidemiological Features of Psychosis

Several literature reviews have addressed the predictive value of various **sub-clinical and clinical features,** seen before the onset of psychotic disorders;

- Premorbid adjustment in adolescents and Global Assessment of Functioning (GAF) in adolescents and adults (before and after First Episode Psychosis, FEP) are the best predictors of diagnosis following a FEP. GAF (before and after FEP) is the best predictor of outcome (adolescents and adults) [10].

[†] This developmental model of psychosis is further discussed in chapter II.

- The strongest risk factor for schizophrenia is familial risk with genetic loading. Other risk factors include pregnancy and delivery complications, infections during pregnancy, disturbances of early neuromotor and cognitive development and heavy cannabis use in adolescence [11].

- Across studies, severity of sub-threshold positive symptoms, poorer social functioning, and genetic risk for schizophrenia appear to be consistent predictors of conversion to psychosis, with algorithms combining these indicators achieving positive predictive power > 80% [12].

- On average 76% (range 46-92.6%) of the UHR patients made *no* transition to psychosis during follow-up (range 6 to 40 months). An older mean age at baseline was associated with significant lower transition rates in publications with follow-ups exceeding 1 year [13].

- In their comprehensive review, *Fusar-Poli et al.* presented findings on clinical predictors of transition to psychosis from high-risk states [6]. The authors concluded that positive predictive values (PPV) ranged from 65 to 86% for various combinations of positive, negative and cognitive symptoms.

- Psychotic Experiences (PE) predict onset of later psychotic disorder (at a rate of 0.6%) per year, particularly if persistent [14]. Of those who report PE, ~20% go on to experience persistent PE whereas for ~80%, PE will remit over time [15].

The role of **cannabis** as a risk factor for psychosis has been widely investigated:

- Early use of cannabis did appear to increase the risk of psychosis (derived odds ratio=2.9, 95% CI=2.4-3.6). For psychotic symptoms, a dose-related effect of cannabis use was seen, with vulnerable groups including individuals who used cannabis during adolescence, those who had previously experienced psychotic symptoms, and those at high genetic risk of developing SCZ [16].

- There is an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio=1.41, 95% CI=1.20–1.65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis most frequently (2.09, 95% CI=1.54–2.84). This is independent of confounding and transient intoxicating effects [17].

Childhood trauma (CT) has been associated with the development of psychosis, as stated by two selective reviews:

- Hallucinations and delusions have been implicated as factors in the relationship between CT and psychosis. This link can take multiple directions: early CT contribute to maladaptive psychological schemas that influence the appraisal of abnormal experiences such as fleeting hallucinations or paranoid thoughts; or alternatively hallucinations and delusions are variants of post-traumatic intrusions, such as flashbacks and nightmares [18].

- The causal association between CT and psychosis is strong (odds ratios in the order of 3) and significant when controlling for genetic risk; reverse causation (psychosis to CT) is unlikely to explain the association. Plausible neurobiological mechanisms linking adverse experiences to psychosis, include sensitization of the mesolimbic dopamine system, changes in the stress-related brain structures and expression of genes regulating mood [19].

Pre-schizophrenia individuals have more **social deficits** compared with controls. Furthermore, beginning in childhood, poor social functioning may be a relatively sensitive and potentially specific predictor of schizophrenia. Key results for each domain of social functioning, which derived from a systematic review of the literature, are summarised here [20]:

- Poor undifferentiated social functioning is a moderately sensitive predictor of SCZ among children aged 7-8 but not during infancy or preschool age.

- Antisocial / externalizing behaviour is a reasonably sensitive and moderately specific predictor of SCZ among children aged 5-12.

- Social withdrawal / internalising behaviour is a moderately sensitive predictor of SCZ, beginning around age 11.

- Peer dislike may be a sensitive but not specific predictor of SCZ among children aged 5-11.

The 3 following clinical studies are mentioned exceptionally, as they focused primarily in **clinical predictors of psychosis**:

- ***The Basel Early Detection of Psychosis Clinical Study (Früherkennung von Psychosen, FEPSY, 2009)*** [21]: the most powerful transition predictors within this population selected were attenuated psychotic symptoms (suspiciousness), negative symptoms (anhedonia / asociality), and cognitive deficits (reduced speed of information processing). With these predictors in mind and considering an integrated model for predicting transition to psychosis, the overall predictive accuracy was 80.9% with a sensitivity of 83.3% and a specificity of 79.3%.

- ***The European Prediction of Psychosis Study (EPPS, 2010)*** [22]: a prediction model was developed and included positive symptoms, bizarre thinking, sleep disturbances, a

schizotypal disorder, level of functioning in the past year, and years of education. With a PPV of 83.3%, diagnostic accuracy was excellent. A 4-level prognostic index further classifying the general risk of the whole sample predicted instantaneous incidence rates up to 85% and allowed for an estimation of time to transition.

- ***The North American Prodrome Longitudinal Study (NAPLS, 2011)*** [23]: three variables were found to be associated with transitions from the at-risk-mental-state to psychosis: high unusual thought content scores; low functioning; and having genetic risk with functional decline. A combination of 2 out of 3 of these features produces a reasonable predictive validity (PPV = 65.4%, specificity = 87.2%).

In summary*, several epidemiological features, ranging from the use of cannabis and childhood trauma, to social deficits and a variety of prodromal psychotic features have been associated with the emergence of psychosis; however, it has not been always possible to establish a clear causal link in these associations.*

1.3. Cognition and Psychosis

Years before the onset of psychotic symptoms, individuals with schizophrenia, as a group, demonstrate mean IQ scores approximately one-half of a standard deviation below that of general population [24].

Cross-sectional investigations of neurocognitive baseline assessments in high-risk samples with unknown conversion status have produced rather inconsistent results. Most convincing evidence has established abnormal performance during processing speed measures (Digit Symbol Coding, Trailmaking Test-B, Stroop Colour Naming), the Continuous Performance Test, verbal working memory measures, verbal memory and learning, and verbal fluency, though negative findings have also been reported in every instance [25].

1.4. Genetics of Psychosis

A number of recent and older reviews of Genome-Wide Association Studies (GWAS) and Copy Number Variants studies (CNV) have attempted to identify candidate genes for schizophrenia (SCZ):

- Associations between Hyman Leucocyte Antigen (HLA) polymorphisms on chromosome 6 and SCZ risk have been evaluated for over 5 decades and re-emerged in the GWAS era, with studies providing statistically significant results [26];
- There is an involvement of the Major Histocompatibility Complex (MHC) genes in SCZ susceptibility [27];

- Risk genes associated with SCZ included zinc finger binding protein 804A (ZNF804A), MHC region on chromosome 6, neurogranin (NRGN) and transcription factor 4 (TCF4) [28];
- Various candidate genetic loci were reported to have significant interactions with environmental factors in increasing SCZ risk [29]; several examples are reported:
  - Gene*Cannabis: COMT Val158Met allele, Protein kinase B gene (AKT1 rs2494732, rs1130233) and LRRTM1 (rs673871), DAT1 gene;
  - Gene*Seasonability of Birth: Human Leucocyte Antigen (HLA)-DR1, MTHFR C677T (rs1801133)
  - Gene*Stress: COMT Val158Met allele, MTHFR C677T;
  - Gene*Childhood Abuse/Trauma: BDNF Val66Met allele;
  - Gene*Obstetric Complications: AKT1 (rs2494735, rs3803300, rs1130233), BDNF (rs2049046, ss76882600), DTNBP1 (rs875462) and GRM3 (rs7808623).

***In summary**, various genetic loci are thought to convey a genetic risk for SCZ / psychosis (including MHC, HLA, COMT, BDNF). Current research attempts to shed light in the convoluted interactions of these loci with environmental factors in increasing SCZ risk.*

1.5. Neuroimaging of Psychosis

A number of recent reviews focused on the neuroimaging profile of prodromal psychosis (the At-Risk-Mental-State (ARMS) or [Ultra]-High-Risk (HR or UHR) for psychosis), chronic psychosis (schizophrenia) and the relatives of psychotic patients.

1.5.1. Reviews of Studies on Prodromal Psychosis Populations

A selective review of *Fusar-Poli et al.* focused on the integration of findings across various imaging modalities (structural, functional and neurochemical imaging) [30]. The authors report their core findings in prodromal psychosis populations:

- Altered prefrontal activation during a task of executive working memory was directly related to striatal hyperdopaminergia; this provided evidence of an association between dopamine dysfunction and abnormal prefrontal function.
- Medial temporal cortical dysfunction (during a memory task) and perturbed glutamatergic neurotransmission, both regarded as fundamental pathophysiological features of psychosis, were not linked.

Additional evidence resulted from two more systematic reviews of studies on HR populations, coming from the same research team. *Smieskova et al.* [31,32] selected studies with structural,

functional and multimodal neuroimaging data of HR populations. They categorised subjects based on (a) the presence of hereditary factors (G-HR) or clinically manifested symptoms (C-HR) and (b) transition (HR-T) or non-transition (HR-NT) to psychosis. The following core results were described:

- *Structural findings*. Deficits in temporal, cingulate and cerebellar regions were seen in G-HR, with additional prefrontal, insular and caudate deficits in C-HR. Progressive prefrontal deficits related to transition to psychosis were noted in C-HR. Decreased prefrontal, cingulate, insular and cerebellar gray matter volume (GMV) was described in HR-T, compared to HR-NT subjects.

- *Functional findings.* Using the cognitive paradigms of working and verbal memory and social tasks, abnormalities in prefrontal, cingulate and middle temporal areas were seen in G-HR, with additional parietal, superior temporal and insular abnormalities in C-HR. Transition to psychosis was more detectable in C-HR and linked to changes in prefrontal, hippocampal and striatal regions. Reduced brain activation in prefrontal and cingulate cortices was described in HR-T, compared to HR-NT subjects. Overall, neurofunctional deficits distinguishing HR subjects from healthy controls were spotted in prefrontal, temporal, parietal, striatal and cerebellar regions, during a variety of cognitive tasks.

- *Multimodal studies* correlated psychotic symptoms with altered prefrontal and hippocampal activation and striatal dopamine and thalamic glutamate function.

The above results were challenged by a recent selective review of neuroimaging findings in the ARMS [33]. *Wood et al.* state that studies in this population show differences from healthy people, but not outside the normal range, and the overall lack of consistency question the utility of neuroimaging in predicting the development of psychosis. However, it was noted that activation of the stress system and increased striatal dopamine synthesis was indicative of later transition to psychosis.

The authors of another review focused on the volume of pituitary gland (reflecting activation levels of Hypothalamus-Pituitary-Adrenal axis) in UHR for psychosis, FEP and SCZ populations [34]. *Nordholm et al.* found a trend of a larger pituitary volume in both Ultra-High Risk (UHR) for psychosis subjects who had transitioned to psychosis and in FEP subjects compared to healthy controls; antipsychotics and female gender were also positively correlated with pituitary volume.

***In summary**, neuroimaging studies on subjects with a proneness to psychosis have revealed structural and functional abnormalities compared to healthy controls. Functional ROIs, found in*

the prefrontal, cingulate and temporal cortices, the insula, the cerebellum and the striatum more frequently show reductions in brain activation, during a variety of cognitive tasks including working and verbal memory and social tasks. Structural ROIs, found in all the above areas, show mainly reductions in GMV.

1.5.2. Reviews of Studies on Schizophrenia Populations

Numerous reviews focused on structural and functional neuroimaging findings of studies of populations with established diagnosis of schizophrenia, and multiple findings are reported below:

- *Anterior cingulate* volumes were significantly reduced in SCZ populations compared to healthy controls [35];
- *White matter tractography:* review of diffusion tensor imaging (DTI) studies in SCZ revealed abnormalities, such as decreased fractional anisotropy (FA) along with increased diffusivity within prefrontal and temporal lobes, as well as abnormalities within fiber bundles connecting these regions (including the uncinated fasciculus, the cingulum bundle and the arcuate fasciculus) [36];
- Structural (loss of asymmetry in diffusion anisotropy in the uncinate fasciculus) and functional (reduced left lateralisation, increased right or bilateral brain activation) abnormalities in brain regions involved with *language perception and processing* were noted in SCZ patients [37];
- Earlier studies In SCZ have observed functional abnormalities in regions known to be critically involved in *social cognition*, such as the medial prefrontal cortex (theory of mind tasks), the amygdala (emotion perception tasks) and the inferior parietal lobes (agency judgments) [38];
- *Negative symptoms* were related to the functioning of the VLPFC and Ventral Striatum. *Positive symptoms*, particularly persecutory ideation, were related to functioning of the medial PFC, the amygdala, and the hippocampus/parahippocampal region. *Disorganization symptoms*, although less frequently evaluated, were related to the functioning of the DLPFC. No symptom domain had a consistent relationship with the middle or superior temporal regions [39];
- A modest under-recruitment of bilateral amygdalae during processing of *emotionally aversive stimuli* has been consistently found in patients with SCZ [40];

- *Cerebellar hypoactivation* was reported in the majority of group comparisons (SCZ vs controls) following an inverted U-shape pattern across ages (maximum hypoactivation noted in the 3rd decade of life) [41];
- Patients with SCZ-spectrum disorders demonstrate ventral striatum (VS) hypoactivation during *reward anticipation* [42];

***In summary**, neuroimaging studies on SCZ patients have revealed a wealth of structural and functional abnormalities compared to healthy controls, involving the prefrontal (DLPFC) and temporal cortices, the amygdala, the hippocampal and parahippocampal regions and the white matter tracts connecting those areas.*

1.6. Shared Biomarkers

Interestingly enough, a number of biomarkers, appear to be shared between SCZ and other psychiatric disorders, such as Attention-Deficit Hyperactivity Disorder (ADHD), Autistic Spectrum Disorders (ASD) and Bipolar Affective Disorder (BPAD):

Cognition: various degrees of executive dysfunction can be seen in ADHD [43], SCZ and less in BPAD [44];

Neuroimaging: GM and WM deficits are shared between ADHD [45], BPAD [46] and SCZ. Decreased thalamic volumes are findings in both ADHD and BPAD; decreased hippocampal volumes are findings in both BPAD and SCZ. Perturbed frontal lobe activation as well as altered connectivity between cortical and subcortical regions are seen in all disorders.

Genetics: BPAD and SCZ share a certain degree of genetic load (ZNF804A, CACNA1C, NRGN, PBRM1) [28]; whilst CNVs are encountered in both disorders, largest deletions and duplications are more likely found in SCZ rather than BPAD. CNVs (such as deletions of NRXN1) as important risk factors for ASD and SCZ, while common SNP alleles are seen in ASD, BPAD and SCZ [47].

1.7. Conclusion

I acknowledge that the majority of biomarkers described so far, cannot be assumed to represent 'predictors' of psychosis. Most of the reviews presented in this chapter, summarise the findings of studies focusing on either genetic or neuroimaging biomarkers of behavioural phenotypes. These studies have primarily included individuals who have already developed psychosis, either at an early or a late stage; and less frequently non-psychotic subjects at risk of developing psychosis. I have however to accept that in the case of chronically psychotic patients, these biological features might very well represent epiphenomena of processes related to the pathophysiology of psychosis, which broadly remain unknown to us, or even be linked to brain alterations, due to the use of psychotropic medications. It is therefore

meaningful that the hunt for biological predictors of mental disorders could initially focus on those brain areas or genetic loci linked to the fully developed disorders, as I can hypothesize that some of those features might predate the development of the illness. To confirm this hypothesis, one will require longitudinal studies on general population, which will aim to identify subjects at UHR for developing an abnormal psychotic phenotype, based on their biological profile.

In the meantime, a number of **epidemiological studies** of clinical features have tried to identify predictors of psychosis. Some of those studies have shown that prodromal psychotic symptoms in combination with the level of premorbid social functioning and the genetic risk for schizophrenia can have a positive predictive power in the area of 80% [12]. It would be of great interest to see more of those studies developed in the future, with a special focus on brain and genetic features.

There is a plethora of **screening tools** developed so far, spotting the pre-psychotic states, designed for children and adolescents populations, and using behavioural data at most. Among the most widely used are the Community Assessment of Psychic Experience – a self-reported questionnaire (CAPE-42) [48] and the CAARMS [49].

There is equally a multitude of **cognitive tasks** employed so far, alone or in combination with functional neuroimaging, for the study of psychotic or UHR populations. Cognitive deficits typically described in psychosis include a *dysexecutive syndrome* which encompasses impairments in working memory, planning, attention span and inhibitory control. In the more recent years, an increasing interest in other aspects of psychosis, such as *social cognition* and *emotion processing* has resulted in the expanding use of *reward tasks* and *face emotion recognition tasks.* As social cognition deficits are seen across the whole spectrum of the psychosis continuum and show strong associations with functional outcomes [50], there is scope for the application of **reward tasks** in the quest for neuroimaging biomarkers. Similarly, as emotion dysregulation is seen at the core of the vulnerability to psychosis [51], use of **face tasks** could also provide important insights during the neuroimaging investigation of related disorders.

Nevertheless, a reasonable observation is that very few (if any) of the proposed 'predictors' of psychosis in any modality (e.g. genetics, neuroimaging) have been submitted to analysis of prediction at the individual level. The status of any biomarker as a 'predictor' has been based on statistical associations which are largely dependent on the design of the study, rather than on empirical proof. When reverse causality is ruled out, a consistent association of X predicting Y, leads to an assertion that for any participant you can predict Y given X. This is exemplified on

the notion of PPV in UHR for psychosis populations, which can be often troubling as PPV depends on the prevalence of the condition; UHR is rare, transition to psychosis even rarer.

There is an increased need to integrate those data into a comprehensive theory, which could account for the pathophysiology and aetiology of psychosis, with implications to early detection, diagnosis and management. A model for this can be the application of multimodal fusion methods in the study of schizophrenia. Various paradigms have been described so far, including function-function (fMRI-EEG/ERP), structure-structure (GM-WM), function-structure (fMRI-DTI), function-genotype (fMRI-SNPs), structure-genotype (sMRI-SNPs) [52]. This approach allows for the study of maps of neuronal connections in human brain (the connectome) to either a cellular level (links with the proteome and genome) or to a macro scale, and could provide a more integrated vehicle to understand psychosis.

1.8. Summary of Biomarkers of Psychosis

Clinical and Epidemiological: prolonged use of cannabis, experience of prodromal psychotic symptoms, deficits in social functioning, traumatic experiences during childhood;

Cognition: reduced IQ scores, deficits in executive functions including processing speed, working memory and verbal fluency;

Neuroimaging: most of the abnormalities identified are shared between SCZ patients and UHR subjects, which places those alterations at the core of the psychosis continuum aetiology.

- *Structural abnormalities:* GM and WM abnormalities, deficits in frontal, temporal and cingulate regions, smaller hippocampal volume.
- *Functional abnormalities:* abnormal prefrontal and temporal cortices activation (fronto-temporal dysconnectivity) during executive and memory tasks, abnormal activation of the amygdalae during emotional tasks and cortico-striatal dysconnectivity during reward tasks.

Genetics: associations with numerous genetic loci (MHC, HLA, COMT, BDNF), which can also interact with environmental factors in increasing the risk of psychosis.

Chapter II: Psychotic-Like Experiences and the CAPE Questionnaire

2.1. PLE, why are they important?

Various terms have been used to refer to the sub-clinical manifestations of the psychosis phenotype, including psychosis proneness, psychotic-like experiences (PLE), attenuated psychotic symptoms (APS) and schizotypy. A **developmental model of psychosis** describes transitory symptoms (psychosis proneness) becoming abnormally persistent (persistence) and subsequently clinically relevant (impairment) [53]. This model is in line with the view that psychotic symptoms are not "all-or-nothing" intrinsically pathological phenomena but fall within the spectrum of normal experiences, referred to as the **extended psychosis phenotype** or **psychosis continuum** [54]. The model is supported by the high prevalence rate of delusional or hallucinatory experiences in the general population, substantially higher that the prevalence rates of psychotic disorders [55]. The model also postulates that PLE are associated with increased risk of future onset of a psychotic disorder, particularly when they are persistent, taking also into account that PLE do not constitute a unitary phenomenon and present in different types with different trajectories and underlying causes [56]. Per this consideration, PLE are overdetermined phenomena in the sense that they might be present for different reasons:

- An expression of an underlying, more fundamental disturbance.
- An expression of 'clinical noise' around a non-psychotic syndrome and not necessarily associated with distress or disability.
- Present in non-clinical 'normal' individuals, not associated with distress or disability or increased vulnerability to psychotic disorder.

As PLE share a number of risk factors with schizophrenia, they offer a useful non-clinical phenotype to study the aetiology of psychotic disorders [57]; furthermore lack of exposure to anti-psychotic agents, and illness chronicity offers a unique opportunity to study the putative neural correlates of psychosis in drug-naïve subjects.

2.1.1. Epidemiology and Aetiology of PLE

The **prevalence of PLE** has been the focus of several literature reviews. A meta-analysis by *Jim van Os et al.* in 2010, revealed that PLE appear to be common in the general population having a median prevalence rate of 5% and a median incidence rate of 3%. Small differences between prevalence and incidence rates, along with data from follow-up studies suggest that 75-90% of PLE are transient and disappear over time [53]. In a similar later review from 2012, *Kelleher et al.* estimated the median prevalence of psychotic symptoms among children aged 9 to 12 at 17% and among adolescents aged 13 to 18 at 7.5% [58]. It appears that PLE, given their broader definition, are expected to present higher rates in the general population, compared to strictly

defined psychotic symptoms. Based on findings from the *Netherlands Mental Health Survey and Incidence Study (NEMESIS),* in years 1996-1999**,** and having access to a sample of 7,076 adults, *Jim van Os et al.* revealed that while 1.5% of this population fulfilled the criteria of a psychotic disorder, 4.2% reported delusions and/or hallucinations and up to 17.5% PLE [59,60].

PLE can vary significantly across different **ethnic groups**; a study based on the *UK Fourth National Survey of Ethnic Minorities*, in years 1993-1994, which obtained an overall sample of 8,063 adolescents and adults, showed substantially reduced rates of hallucinations reported in South Asians (2.3%) and Whites (4%) compared to Caribbean (9.8%) [61].

The **effect of age** in the emergence of PLE was addressed by two large survey studies of more than 2,500 adolescents in Ireland, in years 2009-2010: higher rates of PLE in younger adolescents were reported (21-23%) compared to older ones (7%) [62]. The authors, *Kelleher et al.,* showed that the majority of adolescents who reported psychotic symptoms had at least one diagnosable non-psychotic disorder, however this association was stronger for older adolescents (80%) compared to younger ones (57%).

Risk factors associated with PLE, has also been the focus of several epidemiological studies and population surveys. Cannabis use by the age of 15 and weak psychotic symptoms at age 11 were the two stronger predictors of schizophrenia outcomes at age 26, as shown in the *Dunedin Study*, in late 1980s, a birth cohort study of 1,037 individuals from New Zealand [63]. *Scott et al.*, utilised data from *the Australian National Survey of Mental Health and Wellbeing*, in year 1997, which encompassed an impressive overall sample of 10,461 adults. They reported that 11.7% of this population experiences at least on PLE, and higher rates were associated with younger age, migrants, never being married, being divorced/separated or unemployed, having high levels of urbanicity and low levels of socio-economic status [64]. A later study of 1,261 adolescents from the same authors (also deriving from the *same cohort of the Australian population*) revealed factors such as blended and sole parent families, elevated depressive symptoms, presence of depressive disorder and cannabis used in last month to be highly correlated with hallucinations [65]. Based on the *UK Second National Survey of Psychiatric Morbidity*, in year 2000, *Johns et al.* pooled data from an overall sample of 8,520 adults, and linked the presence of psychotic symptoms to cannabis and alcohol dependence, victimisation, stressful life events, lower intellectual ability and neurotic symptoms; males were more prone to develop paranoid thoughts while females had higher rates of hallucinatory experiences [66].

Apart from **cannabis**, **victimisation** (bullying) is among the risk factor more strongly associated with the presence of PLE. In a study of 2,524 German adolescents, cannabis use increased the cumulative incidence of psychotic symptoms up 4 years later, showing a dose-related effect,

while self-reported trauma at more severe levels was also associated with psychotic symptoms [67,68]. Similarly, in a study of 1,290 adolescents in the Netherlands, bullying and sexual trauma were found to significantly increase PLE [69]. Other risk for PLE are prenatal and perinatal events, especially maternal diabetes [70], urbanicity and cognitive impairments at an early age [71] winter birth [72].

***In summary**, the prevalence of PLE experience in the general population varies widely, with a conservative estimate not exceeding 10%. A variety of risk factors were identified, with most prominent protracted use of cannabis and bullying.*

2.1.2. Screening for PLE

A variety of psychometric scales have been used to assess PLE. The most widely employed and validated is the CAPE (Community Assessment of Psychic Experiences Questionnaire) which was developed *by Jim van Os* and colleagues [73], based on PDI (Peters et al Delusions Inventory) [74]. The extended version of CAPE consists of 42 and is a self-report questionnaire with good reliability and validity [75] allowing for detection of 3 clusters of symptoms (depressive, positive and negative) with good discriminant validity [76]. Alternative 4-factors (with the addition of social delusions) and 5-factors (with a further addition of popular psychic beliefs) models could find utility in further distinguishing positive symptoms [77]. [CAPE questionnaire is discussed in detail in section 2.2]

In a validation study of 334 adolescents, screening of PLEs was performed with the 7-item Adolescent Psychotic-Like Symptom Screener (APSS), a short self-report questionnaire. The study revealed that the question about auditory hallucinations, had an optimum positive and negative predictive value, not only for the tested item, but also for any PLE [78].

It is noteworthy that many clinicians have also expressed reservations to the extent that self-reported PLE genuinely represent attenuated psychotic symptoms (APS). In a study of 123 subjects seeking help at a service for the early detection of psychosis, PLE were assessed with the PDI and the revised Launay-Slade Hallucination Scale (LSHS) and APS were assessed with the Structured Interview for Prodromal Syndromes (SIPS) [79]. It was concluded that the criterion validity of PLE for APS was insufficient, so the prevalence of APS (40.7%) could not be deduced by the larger prevalence of PLE (98.4%). Consequently, the authors considered that the population prevalence rate of APS has to be assumed to be lower than indicated by epidemiological studies of PLE.

A recent systematic review included a total of 76 papers on definition and assessment of PLE. [80]. The review listed a phethora of assessment tools used to quantify for PLE, and comprises excellent and up-to-date summary of the relevant literature. Lee et al. concluded that “as PLE

are poorly understood, there are great variations and assessment tools adopted by different studies". They could not identify a golden standard for the assessment of PLE and they noticed the absence of specific phenomenological definition, as most assessment tools define PLE quantitatively.

***In summary**, a wide variety of tools have been developed so far for the assessment of PLE. Despite inherited limitations, some of these scales, such as the CAPE questionnaire, can provide reliable and valid detection and measurements of PLE.*

2.1.3. Clinical Features of PLE

A variety of psychopathological features have been linked to the presence of PLE. Some examples are described below:

- Poor mental health, suicidal ideation and deliberate self-harm behaviour [81,82];
- Impairments in a verbal theory of mind task were positively associated with schizotypal symptoms and first-rank psychotic symptoms [83];
- Subtle dyskinesia, which was suggestive of a basal ganglia pathology [84];
- Internalising (anxiety, depression, social withdrawal) and externalising (hyperactivity, aggression, antisocial / oppositional behaviour) psychopathology [85];
- Longitudinal deterioration in problematic internet use and reality substitute was linked to the PLE phenotype, despite similar baseline levels [86];
- Mixed- rather than left- handedness was related to psychosis proneness [87];
- Personality traits such as neuroticism (positively linked to all clusters of PLE) and openness to experience (positively linked to persecutory ideas and magical thinking); these associations also survived control for depression [88];

High presence of PLEs, is associated with increased levels of stress which can in turn give raise to reactive psychopathology; however, the nature of these associations remains unknown and needs to be explored further.

2.1.4. Characterisation of PLE

Several studies proposed clusters or dimensions of PLEs. Examples include the following:

- 3-factors model: depressive, positive and negative symptoms [76];
- 2-factors model: schizophrenia nuclear symptoms, schizotypal signs [89];

- 4-factors model: bizarre experiences, perceptual abnormalities, persecutory ideas, magical thinking [90];
- 5-factors model: hallucinations, delusions, paranoia, grandiosity and paranormal beliefs [91,92];
- 6-factors model: paranoia, hallucinations, cognitive disorganisation, grandiosity, anhedonia, parent-rated negative symptoms [93].

This variety of these categorisations can be explained by the use of different tools to assess PLE, or by the variability in the sample studied. It is of note that the 3-factor clustering (positive, negative and depressive cluster) most commonly used with *CAPE-42*, bears a resemblance to the three scales (positive, negative and general psychopathology) of the Positive and Negative Syndrome Scale (PANSS)[94], which is used for assessment of psychotic symptomatology in clinical populations. In my studies I followed this widely adopted 3-factor model, but I also introduced a composite measure consisting of three items (persecutory ideation, bizarre ideas or receiving messages from media and auditory hallucinations) carrying an increased clinical significance and optimal predictive value for transitions to psychosis [see my specific stratification rationale in CAPE 3-Items Score, Specific Stratification].

2.1.5. Neuro-Cognitive features of PLE

Higher rates of PLEs are associated with a number of neuro-cognitive features:

- Verbal fluency deficits: an association observed in men but not in women [95];
- Total IQ score: the association between PLE rates and total IQ score follow an inverted U-shape pattern; however higher PLE rate are more strongly associated with below average IQ than with above average IQ [96];
- Impairments in receptive language, motor and executive function, speed of processing, non-verbal working memory [97,98]; deficits in divided-attention tasks [99];
- Facial Emotion Recognition deficits, especially poor recognition of sad faces [100];
- Individuals with high aberrant salience (the incorrect assignment of importance to neutral stimuli) and low self-concept clarity (clear and internally consistent beliefs about one-self) had the highest levels of PLE [101].

The deficits described above resemble similar findings in psychotic populations and are generally consistent with the neuro-cognitive literature of schizophrenia. This is not surprising,

given that most of the affected cognitive domains are mediated by large regions of the frontal lobes, showing aberrant activation across the whole spectrum of psychotic disorders.

2.1.6. Neuroimaging studies of PLE / UHR for psychosis

A growing number of studies from recent years (2010s onwards) have investigated the neural profile of individuals with high rates of PLE (otherwise labelled as ultra-high risk for psychosis subjects), employing structural and functional neuroimaging methods combined with a variety of cognitive tasks.

- *Jacobson et al.*, the investigators of a study of 25 adolescents, aged 11-13, employed an inhibitory task, and reported that PLE were associated with: (a) Reduced activity within right frontal and bilateral temporal cortex during response inhibition; (b) Reduced activity within the anterior cingulate, insula and middle frontal gyrus during error-related processing; (c) Gray Matter increases within the middle and superior temporal gyri, angular gyrus, orbitofrontal gyrus; (d) White Matter increases along the inferior fronto-occipital fasciculus, cingulum and inferior longitudinal fasciculus [102].

- An additional report comes from *Juckel et al.* who compared 13 young adults with UHR for psychosis to equal number of controls, during a reward test. The authors concluded that compared to the neutral condition, anticipation of reward loss-avoidance elicited significant activation of the ventral striatum (VS) in both healthy subjects and subjects with UHR for psychosis, but there was only a statistical tendency for less activation during loss-avoidance anticipation in prodromal compared to healthy subjects [103].

- In another article, *Roiser et al.* detailed the study of 18 individuals with UHR for psychosis compared to equal number of controls and employing a reward-based salience test, reported that UHR subjects were more likely to attribute motivational salience to irrelevant stimulus features and this bias was related to the severity of their delusion-like symptoms [104]. Ventral striatal responses to irrelevant stimulus features were also correlated with delusion-like symptoms in the UHR group. Striatal dopamine synthesis capacity correlated negatively with hippocampal responses to irrelevant stimulus features in UHR individuals, but his relationship was positive in controls.

- Additional reports derived from a study of 600 undergraduate students screened with the CAPE questionnaire; *Modinos et al.*, identified two groups with high and low PLE (total n=34) who were tested through a number of affective stimuli (neutral pictures, negative pictures) [51]. High PLE subjects showed stronger activation than low subjects in a number of prefrontal regions during reappraisal (reinterpretation of negative pictures, so they no longer elicited negative emotional responses). The amygdala response to negative stimuli

was decreased through reappraisal only in the low group. Functional connectivity analysis revealed less prefrontal-amygdala coupling in high psychosis-proneness subjects. Another study from the same sample (total n=40), employed a multivariate pattern classification based on brain activation during emotional processing and identified group differences within an emotional circuitry including the amygdala, insula, anterior cingulate and medial prefrontal cortex [105]. The authors advocate that emotional dysregulation, thought to result from a disruption in interactions between prefrontal emotion-control regions and subcortical (i.e. amygdala) emotion-generations regions, which is already reported in schizophrenia, can also be seen in UHR populations and might be at the core of vulnerability to psychosis.

- Another research team conducted a study of 21 non-medicated UHR subjects compared to 24 healthy controls [106]. During reward anticipation, the UHR sample exhibited additional activation in the posterior cingulate cortex, and the medio- and superior frontal gyrus. Positive symptoms were correlated with the anticipation signal in the VS and the right anterior insula, while negative symptoms were inversely linked to outcome-related signal within the VS, and depressive symptoms to outcome-related signal within the medial orbitofrontal cortex. The authors, *Wortuba et al., advocate the presence of a reward-associated dysregulation that can be compensated by recruitment of additional prefrontal areas.*

- *Winton-Brown et al.* conducted another study of 29 UHR for psychosis subjects compared to 32 controls divulged that during reward anticipation. UHR subjects showed greater activation than controls in the ventral pallidum bilaterally [107]. Dynamic causal modelling (DCM) revealed that reward-induced modulation of connectivity from the ventral striatum/pallidum to the midbrain was greater in UHR subjects than control, and that in UHR subjects the strength of connectivity in this pathway was correlated with the severity of their abnormal belief. In conclusion, ventral striatal/pallidal function is altered in people with UHR for psychosis and this is related to the lever of their psychotic symptoms.

- Most recently, a study by *Bourque et al.* that utilized a smaller sample from the IMAGEN cohort [‡] revealed that relative to control (n=135), youth with high PLE rates (n=27) at age 14 demonstrated *increased* hippocampus/amygdala activation during processing of neutral faces; *reduced* dorsolateral prefrontal activation (DLPFC) during failed inhibition; *increased*

[‡] My overall sample consisting of 1,434 healthy adolescents, was obtained from the IMAGEN database. This provided neuroimaging, genetic and clinical data of 2,000 healthy adolescents from eight European cities, followed at the ages of 14 and 19. [Details are described in section 4.2.]

anterior/middle cingulate gyrus activation and *decreased* fusiform gyrus activation during the anticipation phase of an MID task [108].

***In summary**, a wealth of neuroimaging studies proclaim a mixture of aberrations in brain activation and connectivity during various cognitive tasks; among the most common findings are reduced activation in DLPFC (including the middle frontal gyri), temporal areas (including the insula and fusiform gyrus) and limbic areas (including the anterior/middle cingulate gyri) during inhibitory control; aberrant hippocampal/amygdala activation during processing of faces; abnormal striatal activation during reward tasks; and disrupted connectivity between prefrontal and subcortical areas during affective tasks. Most of the above-mentioned findings are also reported in SCZ populations, which provides additional evidence for the biological basis of the continuum model of psychosis.*

2.1.7. Clinical Outcome of PLE

Common outcomes associated with PLE are depression, distress and poor functioning; it appears that bizarre experiences and persecutory ideas show greater associations with poor outcome [109-111]. Schizotypy significantly moderated the association between PLE and subjective distress; more PLE reported, yet less distress associated with PLE [112]. Persistence of PLE was associated with a greater use of emotion-oriented coping, whereas a decrease in PLE over time was associated with an increased use of task-oriented coping [113].

2.1.8. PLE and Psychosis

2.1.8.1. Schizophrenia and PLE

Individuals with high rates of PLE have common features with SCZ patients. Non-clinical psychosis phenotype is familial, heritable, co-varies and shares an extensive number of risk factors with schizophrenia-spectrum disorders [57]. PLE and psychotic disorders not only share epidemiological, environmental and developmental risk factors (urbanicity, migration, ethnic minority, socio-economic background, employment/marital status, childhood trauma, victimisation, domestic violence, substance use, obstetric complications, maternal infection, neuro-motor deficits), but also a number of common neuro-anatomical and neuro-functional abnormalities (hypo-frontality, fronto-temporal dysconnectivity, gray and white matter abnormalities), deficits in cognition and language (verbal fluency, receptive/expressive language, speed of processing) and co-morbid psychopathology (depression, anxiety, suicidality, self-harm, antisocial behaviour) [54]. PLE convey an increased risk for the development of psychotic disorder, however there are different types of PLE with different likely trajectories and underlying causes [56]. This observation gives rise to the hypothesis that

PLE and other psychotic disorders, though not unitary phenomena, could have a common genetic basis and consequently share similar dysfunctional neural circuits.

Cognitive impairments in SCZ have been broadly recognised as a core future of the illness [114]. Severe impairments are noted in executive functioning, motor speed and verbal fluency, while moderate impairments are also present in visuo-motor skills and working memory [115]. Furthermore, social cognition can be impaired in schizophrenia [116] and mediates a significant relationship between neuronal activity, cognition and schizophrenia [117].

If PLE and SCZ are part of the same continuum of psychotic disorders, this hypothesis could be extended to encompass cognitive impairments seen within the psychosis spectrum; this could also be further extended to linking some of those cognitive deficits with the aetiology of psychosis. In a recent study of adolescents with an extended psychosis phenotype, the presence of psychotic symptoms was associated with impairment on processing speed tasks and in non-verbal working memory [98]. Another study showed an association of PLE in adolescents with impaired attention on the divided-attention task, which demands increased attentional effort [99]. An EEG study in adolescents revealed a deficit in receptive language (characterised by a reduction in P300 amplitude) related to the presence of PLE [118]. Poor facial emotional recognition was also linked to PLE in a school-based sample of adolescents [100].

A number of various other conditions or traits associated with PLE and discussed already, point towards the direction of linking these symptoms to the development of future psychotic illness. Impairments in the theory of mind may represent a developmental landmark associated with positive schizotypy and PLE [83]. Similarly, schizotypy was found to be associated with more PLE and also to significantly moderate the association between PLE and subjective distress [112]. Both externalising and internalising psychopathology was associated with PLE in a longitudinal general population child cohort [85]. Subtle dyskinesia was associated with higher scores of PLE in a general population sample of 19-year-old participants [84]. Winter seasonality of birth was also having an effect on the presence of PLE in adolescents [72].

***In summary**, common epidemiological and neuro-cognitive features of the PLE and schizophrenia phenotype point towards a link, which can be understood in the context of a unifying psychosis continuum.*

2.1.8.2. FEP and PLE

Studies in patients with first-episode psychosis (FEP) introduced another line of research employing Diffusion Tensor Imaging (DTI) tractography, a specific study of white matter abnormalities. Fractional anisotropy (FA) reductions, a measure of white matter dysconnectivity, were present in two of three main tracts connecting frontal and temporal

regions (namely the superior longitudinal fasciculus and the uncinate fasciculus, but not the cingulum) in FEP subjects [119]. The degree of these abnormalities was also directly associated with clinical short-term outcome. Earlier studies also reported abnormalities of uncinate fasciculus in FEP and recent onset schizophrenia individuals [120,121]. It is of note that reduced left uncinate fasciculus FA was also associated with deficit schizophrenia, thus providing a possible mechanism for the understanding of negative symptomatology [122]. Subjects at risk of psychosis and in FEP share common features of superior temporal lobe dysfunction and fronto-temporal dysconnectivity [123].

***In summary**, If PLE represent a prodromal psychotic phenotype, subjects with PLE are anticipated to share some of the neuro-imaging findings of FEP, such as fronto-temporal dysconnectivity.*

2.1.8.3. UHR for Psychosis and PLE

A significant number of studies have focused on subjects of ultra-high-risk (UHR) for developing psychosis, aka the at-risk mental state (ARMS) during the last decade. In the general population, mixed and non-specific expression of psychosis, depression, anxiety and sub-threshold mania is common and mostly transitory. When combined with distress, it may be considered as the first, diagnostically neutral stage of potentially more severe psychopathology, which only later may acquire a degree of diagnostic specificity and possible relative resistance to treatment [124]. UHR for psychosis status is recognised as part of the extended psychosis phenotype, with prevalence estimated at 7.5% [14]. This stream of research is in line with the neurodevelopmental model of schizophrenia; the roots of the disorder lie in the abnormal development and maturation of the central nervous system [125,126].
Contemporary data suggest that rates of subjects at UHR that will eventually progress to psychosis range between 18% (at 6 months follow-up) and 36% (at more than 3 years follow-up) [127] . Neuropsychological and brain imaging findings are described in the early stages of psychosis and schizophrenia [128]; this gives rise to the hypothesis that there are a number of processes at psychosis onset that may represent biomarkers of future illness. These neurobiological markers focus on maturational processes, implicating the integrity of frontal and temporal cortices.

Neurocognitive data: Among other studies, a longitudinal cohort of 230 individuals followed up for 7 years on average, identified poorer neuro-cognitive performance on verbal learning and memory, processing speed and attention and verbal fluency, as predictors of poor functional outcome [129].

Neuroimaging data: A series of neuroimaging studies employing sMRI, fMRI and Positron Emission Tomography (PET) revealed that increased vulnerability to psychosis is associated with brain changes, which are qualitatively similar to those seen in psychotic disorders and appear inter-related [130-132]. More specifically, UHR subjects showed reduced prefrontal volume; differential activation in prefrontal and medial temporal cortex; altered connectivity and reduced white matter integrity in fronto-temporal pathways; reduced thalamic glutamate levels; and elevated striatal dopamine function. Clinical follow up at 24 months revealed that reduced medial temporal volume, increased prefrontal, medial temporal, and midbrain activation, and elevated dopamine function at baseline predicted later onset of illness. Comparison of baseline and follow up scans indicated that the onset of psychosis was associated with longitudinal decreases in medial temporal volume and in thalamic glutamate levels, and increases in striatal dopamine function. Findings from another sMRI study revealed cortical thinning in the prefrontal cortex, anterior cingulate cortex, inferior parietal cortex, parahippocampal cortex and superior temporal gyrus, areas that correspond to the structural abnormalities found in schizophrenia [133]. If PLE represent indeed an UHR for psychosis, I would expect similar brain changes in individuals with this phenotype. [Please refer to section 2.1.6. for more details]

Transition to psychosis in UHR individuals is associated with prefrontal and subcortical dysfunction. In a 2-year follow-up study, UHR subjects who subsequently developed psychosis, showed increased activation in bilateral prefrontal cortex (PFC), midbrain/basilar pons, the left hippocampus, greater midbrain-PFC connectivity and elevated brainstem dopaminergic function [134]. Review of the literature suggest that (a) vulnerability to psychosis is associated with consistent grey matter (GM) decreases in prefrontal and temporo-limbic areas (b) the onset of full disease is accompanied by temporo-insular, anterior cingulate and cerebellar GM reductions (c) alterations in temporal regions underlie the clinical onset of psychotic symptoms [135]. All the above-mentioned brain areas have attracted increased scientific interest, towards identifying biomarkers of psychotic illness.

In summary*, PLE represent the clinical manifestation of the UHR for psychosis phenotype, which in turn conceptualizes a group of individuals with increased risk of transition to psychosis. Those individuals initially present with subtle prodromal psychotic symptoms; however, they can also have a variety of neurocognitive deficits and associated neuroimaging findings which are consistent with similar features seen in psychotic patients.*

2.1.8.4. Progression to Psychosis and PLE

A wealth of research, over the past 3 decades, supports the hypothesis linking the presence of PLE with the emergence of future psychotic disorders:

- High scores on perceptual abnormalities and magical thinking in adolescence predicted psychosis 10 years later [136];
- Self-reported psychotic symptoms at age 11 predicted a high risk of schizophreniform diagnosis at age 26 [137];
- Exposure to baseline psychotic symptoms and urbanicity together doubled the rates of such experiences following a 3.5 years follow-up [138].
- The 3-year persistence rates of PLE varied between 26% (***NEMESIS***) and 31% (***EDSP***), while the presence of developmental exposures (cannabis, trauma, urbanicity) increased rates of such persistence up to 83% and 51% respectively [139];
- High levels of PLE at age 5 and 14 predicted high levels of delusional-like experiences at age 21 [140,141];
- Persistent subclinical psychosis for 3 years increases the risk of transition to clinical psychosis at >8 years in a dose-response fashion [142];

Developmental trajectories of PLE have also been the focus of more recent studies. A large study of more than 7,500 adolescents (***TRAILS***) revealed four groups with distinct developmental trajectories of mild positive psychotic experiences (*mild, decreasing, intermittent, persistent*) [91,92]. The persistent trajectory was associated strongly with cannabis use, childhood trauma, developmental problems and ethnic minority status, and consistently displayed strong associations with factors known to predict transition from subclinical psychotic experiences to clinical psychosis. A similar study with a smaller sample of 409 adolescents showed instead three developmental trajectories of PLE: a *low*; an *increasing* (associated with use of tobacco, cocaine, cannabis and drugs); and a *persistent* (associated with frequent victimisation and elevated depression and anxiety scores) [143]. A birth cohort of 7,387 adolescents (***ALSPAC***) showed that the majority (80.6%) presented with *low* PLE rates, while those with higher rates progress to either a *decreasing* (1.7%), *intermittent* (16.8%) or *persistent* (0.9%) trajectory of PLE and were more likely to come from adverse backgrounds and have disturbed childhood development [144].

In their discussion article, *Spauwen and van Os* employed the psychosis proneness model to account for the association between high rates of exposure to urbanicity and psychosis [145]. They suggested that a number of environmental factors (urbanicity) interact with genetic risk factors to lead to increased rates of expression of psychotic phenotypes, reaching a first peak at puberty. Besides, the presence of an urban environment appears to perpetuate high rates of psychosis, with contrast to a rural one.

***In summary**, presence of PLE infers an increased risk of transition to psychosis, which can be further potentiated by environmental risk factors, such as use of cannabis, psychological trauma and urbanicity. Early detection of PLE, in combination with other biomarkers, is therefore paramount to identify subjects at UHR for psychosis and accordingly implement early interventions, which could potentially deter UHR subjects from developing psychosis.*

2.1.9. Summary of PLE

The concept of PLE has found applications as:

- Evidence for the developing character of psychotic symptoms, ranging from pre-clinical / prodromal (PLE) to clinical (psychotic symptoms) manifestations.
- A non-clinical paradigm in pursuit of the aetiology of psychosis, consistent with the neuro-developmental model of psychosis (interaction between genetic and environmental risks).
- A tool to detect early indications of proneness to developing a future psychotic illness, in accordance with the continuum model of psychosis (UHR for psychosis or the ARMS).

Research in the field of PLE could be informed by related research in FEP and UHR for psychosis populations. The hunt for biomarkers related to PLE is relevant and exciting, and use of functional neuroimaging can provide a useful path to this direction. This emphasized the importance of my research in investigating the neural correlates of PLE.

2.2. The Community Assessment of Psychic Experience Questionnaire

The Community Assessment of Psychic Experiences Questionnaire (CAPE) was developed by Jim van Os and colleagues [73], based on Peters et al Delusional Inventory (PDI) [74], as a screening tool for the detection of PLE in the general population.

CAPE is an extended though self-explanatory and easily self-administered questionnaire. In its extended form, it consists of 42 items, which can be grouped in three dimensions of symptoms: positive (bizarre and social delusions), negative and depressive. CAPE 42 has adequate validity and reliability in detecting these clusters of symptoms in non-clinical populations. A detailed description of CAPE-42 questionnaire (which was used in my studies) can be found in APPENDIX I.

Table 1: CAPE-42 Clusters

1 Depressive Symptoms		2 Positive Symptoms				3 Negative Symptoms	
		2a	Bizarre Symptoms	2b	Social Delusions		
Q1	Sad	**Q5**	Messages from Media	**Q2**	Double Meaning	**Q3**	Not animated
Q9	Pessimism	**Q15**	Telepathy	**Q6**	False Appearance	**Q4**	Not talkative
Q12	No future	**Q17**	Influenced by devices	**Q7**	Being persecuted	**Q8**	No emotions
Q14	Not worth living	**Q20**	Voodoo	**Q10**	Conspiracy	**Q16**	No interest in others
Q19	Frequently Crying	**Q22**	Odd Looks	**Q11**	Being important	**Q18**	Lack of motivation
Q38	Guilty	**Q24**	Thought Withdrawal	**Q13**	Being special	**Q21**	No energy
Q39	Feeling a failure	**Q26**	Thought Insertion			**Q23**	Empty mind
Q40	Feeling tense	**Q28**	Thought Broadcasting			**Q25**	Lack of activity
		Q30	Thought Echo			**Q27**	Lack of emotional intensity
		Q31	External Control			**Q29**	Lack of spontaneity
		Q33	Auditory Hallucinations			**Q32**	Blunted emotions
		Q34	Voices Conversing			**Q35**	Lack of hygiene
		Q41	Capgras			**Q36**	Unable to finish
		Q42	Visual Hallucinations			**Q37**	Lack of interests

2.2.1 Validation Studies of the CAPE

The ***Athens Study of Psychosis Proneness and Incidence of Schizophrenia (ASPIS),*** in year 2001, explored schizotypy and psychosis dimensions in newly recruited air force conscripts in

Greece. Using a sample of 932 young men, the authors of a validation study measured experiences of positive, negative and depressive features of psychosis [76]. Confirmatory factor analysis (CFA) revealed that a three-factor model was a better fit to the data. All three dimensions co-varied with each other, with correlations between the three dimensions in the range of 0.7, and correlation between the dimensions of frequency and distress (severity) was 0.71. The CAPE positive symptom score displayed stronger association with the Perceptual Aberration Scale (PAS) and the Symptom Checklist (SCL-90) Paranoia Subscale; the CAPE negative symptom score displayed stronger association with the Schizotypal Personality Questionnaire (SPQ); and the CAPE depressive symptoms score displayed stronger association with the SCL-90 Depression Subscale.

A large cohort of 31,822 adult Swedish women, taking part in the follow-up phase of the ***Scandinavian Women's Lifestyle and Health Cohort***, in year 2003/2004, gave rise to another validation study. Factorial analysis of CAPE data, which focused on the positive psychotic experience items resulted in five separable but correlated trait dimensions, which reflected the presence of paranoia, grandiosity, magical thinking delusions and hallucinations [146]. High scores on any dimension were associated with a higher probability of questionnaire-assessed lifetime major depressive episodes or generalised anxiety disorder (only to a smaller degree for grandiosity). A similar study from the same authors in a large sample of 1,012 Swedish young adults and adolescents who completed the CAPE online, supported a three-factorial structure for PLE, including paranoia, delusions and hallucinations and excluding grandiosity and common paranormal beliefs [147].

The ***Continuum of Mental Disorders Study (COMED),*** in year 2006, was a longitudinal family study based on the general population of the city of Sittard, the ***Netherlands***. Utilising a validation sample of 765 individuals (510 at follow-up), the authors compared CAPE42 scores with Brief Psychiatric Rating Scales (BPRS) scores and Structured Interview for Schizotypy (SIS-R) outcomes at baseline and follow-up (7.7 months) [75]. Self-reported positive and negative dimensions of psychosis (CAPE42) at baseline were specifically and independently associated with their equivalent interview-based dimensions (BPRS and SIS-R) at follow-up (standardised effect sizes 0.4-0.5). [Please refer to the following section for more details]

A team of researchers from Canada, in 2007, performed a validation study by examining the internal consistency of the CAPE questionnaire in a sample of 2,275 individuals from the general ***Montreal community***, who completed it in either French or English [77]. The internal consistency of all three subscales (positive, negative, depressive symptoms) was good, with Cronbach's coefficient alpha equal to 0.822; 0.805 and 0.795 respectively. CFA showed

Adjusted Goodness of Fit Indices (AGFI) close to 0.90, indicative of a good fit between the observed sample covariance matrix against the matrix estimated from a null model.

The ***Genetic Risk and Outcome of Psychosis (GROUP)*** project, in year 2011, was a longitudinal observational study in the ***Netherlands***, focusing on the factors that make people vulnerable to develop psychosis. A validation study from this sample investigated the psychometric properties of CAPE questionnaire and SIS-R and aimed to enhance measurements through the use of multidimensional measurement models [148]. Data were collected in 747 siblings of schizophrenia patients and 341 healthy controls. Both instruments showed good psychometric properties and were measurement invariant across siblings and controls. The latent traits measured by the instruments showed a correlation of 0.62 in siblings and 0.47 in controls. [Please refer to the following section for more details].

An additional validation study from ***Spain***, in year 2012, utilised a sample of 660 students and 97 patients with psychosis. [149]. Exploratory factor analysis (EFA) supported a three-dimensional model which was different from the traditionally used dimension (positive, negative and depressive symptoms). Internal consistency values for these new dimensions ranged between 0.78 and 0.89 in the sample of students and between 0.84 and 0.93 in the sample of patients. A similar study from ***Chile***, in year 2015, explored the dimensionality of CAPE-15, a shortened version of CAPE-42 questionnaire, in a sample of 727 secondary school students and 245 university students [150]. Applying an Exploratory Structural Equation Models (ESEM) approach, *a best fit was shown for a hierarchical model, composed of a general factor plus three specific factors (persecutory ideation, bizarre experiences and perceptual abnormalities)*.

A cross-sectional online survey of 1,610 ***Australian*** university students, in year 2013, examined the internal structure of the positive scale of CAPE-15 [151]. A three-factor model, including persecutory ideation, perceptual abnormalities and bizarre experiences, produced the best fit, with high levels of internal consistency.

Researchers from the ***Netherlands***, in year 2014, estimated Measurement Invariance (MI), comparing a sample of CAPE questionnaires assessed by paper and pencil (n=796) to a sample of questionnaires assessed by the internet (n=21,590) [152].The findings did not support measurement invariance with respect to assessment method. However, internet sample members who scored 2 standard deviations above average (so with a high vulnerability for psychotic symptoms) would be expected to score 4.8 points lower on the CAPE total score.

Finally, a recent meta-analysis from 2016, focusing on the psychometric properties of CAPE scores (reliability and validity), included 18 factor analytic studies to study CAPE's internal reliability [153]. The authors concluded that CAPE scores were psychometrically reliable and a 3-

factor model, consisting of positive, negative and depressive subscales was supported; a three-parties structure for both the positive dimension (consisting of bizarre experiences, delusional ideations and perceptual abnormalities) and the negative dimension (consisting of social withdrawal, affective flattening and avolition) were also supported.

***In summary**, the plethora of validation data suggest that CAPE questionnaire has a good validity, reliability and internal consistency, in detecting psychotic experiences in non-clinical populations and could be used as a simple and cost-effective instrument to identify individuals at increased risk of developing psychosis.*

2.2.2. Longitudinal Cohorts employing the CAPE

2.2.2.1. EFPTS

The ***East Flanders Prospective Twin Survey in Belgium (EFPTS)*** has prospectively recorded all multiple births in the province of East Flanders since 1964. The final sample consisted of 566 female subjects (283 pairs of twins, 172 monozygotic -MZ and 111 dizygotic -DZ) with mean aged of 27.3 years (aged 18-45). Participants were interviewed five times (T0-T4) at approximately 3- to 4-monthly intervals. CAPE questionnaire was used to assess subclinical psychotic experiences, while the Structured Clinical Interview for DSM Disorders (SCID) and the Symptom Checklist (SCL-90-R) were also used to validate psychotic experiences. Some of the Some of the reported findings were:

- Cross-twin, cross-trait analysis was conducted to investigate the association between repeated continuous measures of self-reported psychotic experiences (assessed with CAPE) in one twin and clinical interview categorical measures of psychotic symptoms (assessed with SCID-I), in the other twin. The results showed that in MZ but not DZ pairs the cross-twin associations were large, significant and of similar magnitudes as the within-twin associations, both showing validity of CAPE and revealing a genetic effect. In addition, the cross-twin associations were significantly larger for younger MZ twins than older MZ twins, providing evidence for a developmental effect [154].
- An investigation of the patterns of developmental course of subclinical psychotic experiences revealed a *Persistent* and a *Low* group with regard to the expression of subclinical psychotic experiences. The Persistent group reported significantly higher levels of depressive and negative symptoms and worse functioning in daily life. Childhood trauma and stressful life events over the study period predicted inclusion in the Persistent group. 45% off the MZ twins of the Persistent group, had also a co-twin in the same group [155].

- 508 female twins completed both prospective and retrospective questionnaires regarding childhood adversity and psychotic trait liability. The effect of childhood adversity was significantly moderated by genetic vulnerability for depression. This moderation was mediated by depressive experience but not by stress sensitivity [156].

- CFA in the female twin sample, replicated a five-dimensional model best describing the phenotype of positive psychotic experiences, consisting of Hallucinations, Delusions, Paranoia, Grandiosity and Paranormal Beliefs [157].

- The Experience Sampling Method (ESM; repetitive random sampling of momentary emotions, psychotic experiences and context) was used to assess emotional and psychotic daily life stress reactivity. Higher levels of emotional stress reactivity (a decrease in positive and an increase in negative affect in response to stress), and increased psychotic reactivity to daily stress was found in individuals with persistent psychotic experiences over time compared to individuals with transient psychotic experiences [158].

2.2.2.2. HBSC

The ***Health Behaviour in School-Aged Children study (HBSC)***, was a general population study aiming to investigate the health, health behaviours and the relevant social context of youth in Europe and North America. The sample consisted of 5,422 adolescents aged 12-16, assessed between October and November 2005. The CAPE questionnaire was used to assess psychotic experiences. Some of the reported findings were:

- EFA followed by CFA in two large adolescent general population sample (5,422 and 2,230 individuals) suggested that psychotic experiences were best represented by 5 underlying dimensions: hallucinations, delusions, paranoia, grandiosity and paranormal beliefs. Prevalences differed strongly, hallucinations having the lowest and paranoia having the highest rates. Girls reported more experiences on all dimensions, except grandiosity, and from age 12 to 16 years, rates increased. Hallucinations, delusions, and paranoia, but not grandiosity and paranormal beliefs, were associated with distress and general measures of psychopathology [159].

- In a cross-sectional sub-study of 4,552 adolescents, an association between cannabis use and subclinical positive symptoms was confirmed and remained significant after extensive adjustment for potential confounders. Strongest associations noted for the discontinued use group and the heavy use group [160].

2.2.2.3. COMED

The ***Continuum of Mental Disorders study (COMED)*** was a longitudinal family study based on the general population of the city of Sittard, the Netherlands, in year 2006. The study comprised 2 measurement points: T1 and T2, with a mean interval of 7.7 months between them. The total general population sample for T1 comprised 768 participants aged 17-77 years, pertaining to 116 families. CAPE questionnaire was among the tools used to assess this population of genetically related individuals, also including Cognitive Failure Questionnaire (CFQ) and SIS-R. Some of the reported findings were:

- Proneness to subjective cognitive failures possibly contributes to the development of persistence of negative symptoms and can be seen as potential risk factor for negative symptoms of psychosis. This overlap was due to individual effects rather than familial liability [161].

- Comparing this general population sample with different patient groups in a community mental health service (suffering with either psychotic, mood or anxiety disorders), resulted in significant differences in positive psychosis items scores. Patients with psychotic disorders had the greatest difference in positive psychosis items compared to non-patients, whereas patients with mood and anxiety disorders had the highest depressive symptom scores and positive symptom scores that were intermediate to that of non-psychotic patients and patients with psychotic disorders [162].

2.2.2.4. GROUP

The ***Genetic Risk and Outcome of Psychosis project (GROUP***) was a longitudinal observational study in Netherlands, in year 2011, focusing on the factors that make people vulnerable to develop psychosis. The full GROUP sample (data release 2.0) consisted of 1,100 patients with psychotic disorders, 1,057 healthy siblings of these patients, 919 parents of these patients, 19 parents of patients who were also diagnosed with psychotic disorder, 562 healthy controls and 27 parents of these healthy controls. Eligible healthy individuals who took part, were aged 18-50, free of psychotic illness and had no first-degree family member with a lifelong psychotic disorder. CAPE and SIS-R were the main tools used to assess this population. Some of the reported findings were:

- 217 patients with psychotic disorders, 281 of their siblings and 176 healthy individuals were assessed according to the Five-Factor Model (FFM) personality traits by using the Neuroticism-Extraversion-Openness Five-Factor Inventory (NEO FFI). Clinical psychotic symptoms were assessed by using the Positive and Negative Symptoms Scale, whereas sub-clinical symptoms were assessed by the CAPE questionnaire. Particularly lower

agreeableness, and to a lesser degree, higher neuroticism and lower extraversion were associated with more severe symptoms in patients. Furthermore, higher neuroticism and higher openness were associated with higher levels of subclinical psychotic experiences in all three groups. Strongest associations were noted in patients. These findings were suggestive that levels of neuroticism increase with the level of familial risk for psychosis [163].

- 813 healthy siblings of patients with a non-affective psychotic disorder, 822 patients and 527 healthy controls were examined with regards to depressive symptoms and their association with positive and negative symptoms. Depressive episodes in all three groups were assessed by the Comprehensive Assessment of Symptoms and History (CASH). Positive and negative symptoms were assessed by the CASH in the patient group, and by CAPE questionnaire in siblings and healthy controls. Patients reported more lifetime depressed mood and more depressive episodes than both siblings and controls. Siblings had a higher chance of meeting lifetime depressive episodes than the controls; no significant differences in depressed mood were found between siblings and controls. In all three groups, the number and duration of depressive symptoms were associated with sub-clinical negative symptoms. In patients and siblings, the number of depressive symptoms was furthermore associated with sub-clinical positive symptoms. Finally, lifetime depressed mood (but not depressive episodes) showed familial clustering [164].

2.2.2.5. TRAILS

Tracking Adolescents' Individual Lives Survey (TRAILS), was a prospective cohort study among adolescents in the Dutch general population. The three data collection waves were T1 (2001-2002, N=2,230, mean age 11.1 years); T2 (2003-2004, N=2,149, mean age 13,6 years) and T3 (2005-2007, N=1,816, mean age 16.3 years). CAPE questionnaire was used to assess psychotic experiences at T3. Parental psychopathology was measured with the Brief TRAILS Family History Interview. Some of the reported findings were:

- General parental psychopathology was associated with CAPE score (OR = 1.08; P < 0.043 for highest quintile) and suggestively predicted psychosis persistence (OR, 1.16; P < 0.072). Psychotic parental psychopathology was suggestively associated with CAPE score (OR, 2.25; P < 0.063 for highest quintile), predicted membership of the Persistent group (OR, 3.72; P < 0.039) and suggestively predicted membership of the Decreasing group (OR 2.04; P < 0.051). Childhood trauma was associated with CAPE score and with all developmental trajectories of subclinical psychosis. There was no evidence of an interaction between trauma and parental psychopathology [165].

2.2.2.6. GNPS

The ***Greek National Perinatal Survey (GNPS)*** was a prospective study of all 11,048 births throughout Greece conducted in April 2013. The Greek Birth Cohort derived as a longitudinal data collection of this sample during years 1990 (6,594 children aged 7) and 2001 (3,500 individuals aged 18). CAPE questionnaire was used in adolescents to capture variation in the positive and negative dimensions in non-clinical psychotic experiences, and additionally in depression. Some of the reported findings were:

- The use of cannabis was positively associated with both positive and negative dimensions of psychosis, independent of each other, and of depression. An association between cannabis and depression did not survive adjustment for the negative psychosis dimensions. First use of cannabis below age 16 years was associated with a much stronger effect than first use after age 15 years, independent of life-time frequency of use. The association between cannabis and psychosis was independent of the distress associated with the experiences [166].

- A significant adjusted interaction between childhood maltreatment and later cannabis use was evident, indicating that the psychosis-inducing effects of cannabis were stronger in individuals exposed to earlier sexual or physical mistreatment [167].

2.2.2.7. Summary of Longitudinal Cohorts

Six longitudinal cohorts of non-clinical populations from the Netherlands, Belgium, Greece and Europe / North America employed CAPE questionnaire to measure prodromal psychotic manifestations. Those studies confirmed several clinical and epidemiological features (cognitive deficits, depressive features, use of cannabis, childhood trauma, parental general and psychotic psychopathology) as risk factors predisposing to the future emergence of psychosis. On the opposite direction, the psychosis proneness phenotype was also associated with increased rates of depressive and negative symptoms, as raised levels of distress and general psychopathology. Taken together, this wealth of data supports the use CAPE as an excellent tool for the measurement of PLE in longitudinal designs.

2.2.3. Other Exploratory Studies with the CAPE

The CAPE questionnaire was used in a non-clinical population of 632 female student subjects in France, to explore the pattern of associations between cannabis use and dimensions of psychosis. Three correlated dimensions of positive, negative and depressive experiences were identified using principal components factor analysis. The frequency of cannabis use was independently associated with the intensity of both positive and negative psychotic experiences. No significant association was found between cannabis use and the depressive

dimension, or between alcohol use and any of the three positive, negative and depressive dimensions [168].

A study 140 young non-psychotic help-seekers (the PACE clinic, Melbourne, Australia), employed CAPE scores to identify subtypes of PLE and their associations with poor clinical outcomes. Three factors were identified: bizarre experiences, persecutory ideas and magical thinking; the first two showed the strongest associations with distress, depression and poor functioning [169]. Similar results were noted in a much larger cohort of 1,882 high-school and university students from Australia, during a cross-sectional survey conducted from the same authors [full set in [170], subsets in [90,171]]. Among the four factors identified, bizarre experiences and paranoid ideation were more strongly associated with distress, depression and poor functioning than perceptual abnormalities and grandiosity.

Investigators of a Swedish study examining a large sample of 1,012 adolescents and young adults, scrutinised the relation between Working Memory (WM), assessed with two online computer tasks, and PLE, assessed with the CAPE. Low WM capacity was modestly associated with increased reports of bizarre experiences and depressive symptoms, after controlling for age, gender and global symptoms scores. When analysis focused on age groups, low WM was exclusively associated with bizarre experiences in young adults and with depressive symptoms for older adults [172].

Finally, researchers from Spain conducted an experimental study of 54 patients with a First Episode Psychosis (FEP) and 150 healthy subjects in order to assess the presence of speech illusion in neutral white noise. For the assessment of psychopathology, PANSS was used in patients and SIS-R and CAPE questionnaire in controls. Patients had a much higher rate of speech illusions, which was only partly accounted by differences in IQ. Differences were particularly marked for signals in random noise that were perceived as affectively salient. Speech illusion tended to be associated with positive symptoms in patients, particularly affectively salient illusions. In controls, speech illusions were not associated with positive schizotypy or self-reported psychotic experiences [173].

***In summary**, a number of exploratory studies have employed CAPE to examine associations between various symptom clusters (positive / negative / depressive or bizarre / persecutory / magical ideas) and several epidemiological and clinical features (use of cannabis, functional outcomes, general psychopathology) in normal individuals.*

2.2.4. Studies on Cut-Off Levels of the CAPE

During a study of 246 Dutch patients having a first contact with mental health services, CAPE-42 scores were used as a screening tool for FEP. A total 26 patients were diagnosed with

psychosis according to the Mini Schedule for Clinical Assessment in Neuropsychiatry (Mini SCAN). Only 10 of them were recognised by clinical routine, and 16 psychotic patients were not properly identified. Using an optimal cut-off value of 50 on the frequency or distress dimension of the positive subscale of the CAPE-42 detected 14 of these misdiagnosed patients. The sensitivity at this point was 77.5 and the specificity 70.5 [174].

An additional report of 165 individuals aged 13-24 years who were referred to an early intervention outpatient service in Vienna, compared scores of the CAPE and the Comprehensive Assessment of At-Risk Mental State (CAARMS) [48,175]. Of the overall sample, 50.9% of individuals were CAARMS-positive and 49.1% were CAARMS-negative. The Receiver Operating Characteristic (ROC) analysis provided the following cut-off points [§]:

- The cut-off value of **2.20** on the positive dimension (frequency + distress, 20 items) showed a sensitivity of 67%, a specificity of 73%, a positive predictive value of 72% and a negative predictive value of 68%.
- The cut-off value of **1.80** on the positive dimension (frequency + distress, 20 items) showed a sensitivity of 83%, a specificity of 49%, a positive predictive value of 63% and a negative predictive value of 74%.
- The cut-off value of **0.47** in the positive dimension (frequency, 15 items) showed sensitivity of 77%, specificity of 58%, a positive predictive value of 66% and a negative predictive value of 71%.
- The cut-off value of **0.47** in the positive dimension (distress, 15 items) showed sensitivity of 73%, specificity of 63%, a positive predictive value of 69% and a negative predictive value of 66%.

***In summary**, the CAPE questionnaire can have potential applications as a tool for the detection of transition to psychosis; cut-off values widely vary across settings and depend on the different sub-scales used. It is of note however that a positive dimension frequency + distress cut-off value in the area of 2.0 / CAPE item provides adequate positive predictive value for transition to psychosis. Special care was taken during stratification in my studies, so my high PLE groups scored above this threshold, thus qualifying as an equivalent to the psychosis proneness phenotype. More extended longitudinal cohorts are required in order to ascertain CAPE as a predictive tool for psychosis and determine cut-off levels suggestive of a high risk for such a transition.*

[§] Cut-off values were calculated per CAPE item and adjusted to the rating convention we applied in my studies: frequency + distress [0-7]; frequency [0-3]; distress [0-4].

2.2.5. Summary of CAPE

CAPE questionnaire has a good validity, reliability and internal consistency, in detecting PLE in non-clinical populations and could be used as a simple and cost-effective instrument to identify individuals at UHR for psychosis. Data from well-known cohorts support the use CAPE as an effective tool for the measurement of PLE in longitudinal designs. Similarly, exploratory studies have employed CAPE to examine associations between various symptom clusters and several epidemiological and clinical features in normal individuals. CAPE can have potential applications as a tool for the detection of transition to psychosis; however, calculating cut-off values widely varies across settings and depends on the different sub-scales used. These observations confirm my choice to use CAPE questionnaire as a measuring tool for PLE in my studies, and to base the stratification of my samples on the scores that this questionnaire generated.

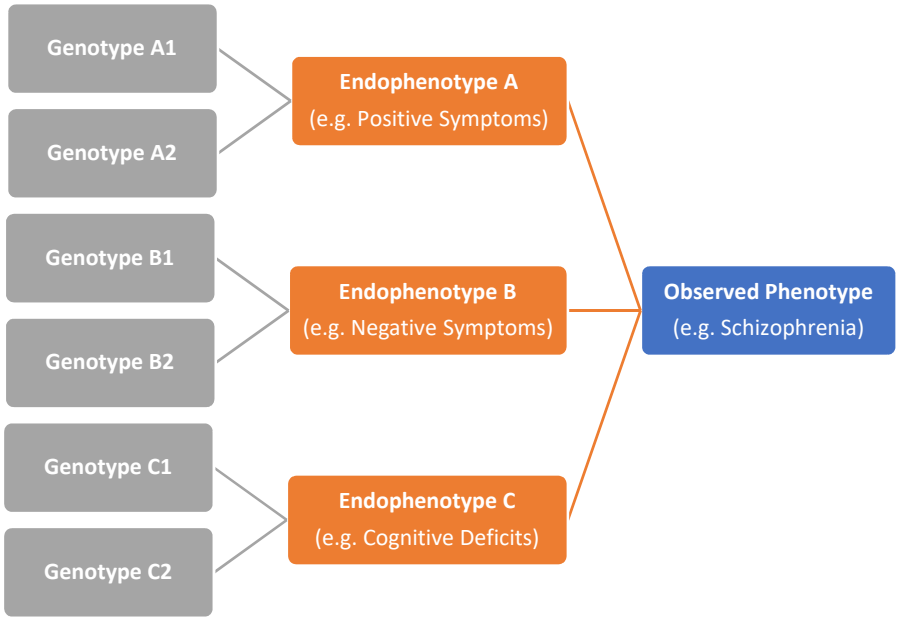
Chapter III: Cognitive Tasks and the Neuroimaging of Schizophrenia

3.1. Cognitive difficulties in Schizophrenia

Usually seen as the 'last frontier' in the treatment of schizophrenia, cognitive difficulties have long been recognised as part of the various clinical presentations of the illness. Since Emil Kraepelin coined the term 'dementia praexox', he implied that a certain degree of cognitive decline should be viewed at the core of psychotic symptomatology. Patients with schizophrenia suffer with various degrees of deficits in several cognitive domains, which usually present from an early age; these include *mild impairments* in perceptual skills, recognition memory and verbal IQ, *moderate impairments* in attention, recall and working memory and *severe impairments* in executive functioning, verbal fluency and motor speed [176]. Impaired cognition together with negative symptoms are the major cause of the marked functional disability that is often associated with schizophrenia [177].

Cognitive differences between schizophrenia patients and healthy people have emerged systematically during decades of neuropsychological research, pointing towards the presence of endophenotypes within the broad schizophrenia population [178]. Poor ***phenotype definition*** was recognised as one of the main obstacles for aetiological research in schizophrenia [179]; thus, neuro-cognition might be the vehicle to investigate the heterogeneity of this complex disorder. Employing functional neuroimaging in combination with neurocognitive testing, can reveal dysfunctional brain networks associated with particular cognitive deficits and also help to elucidate the potential neural correlates of some of the broader schizophrenia psychopathology.

Figure 1: From Genotypes to Endophenotypes and Single Phenotypes.



Multiple genotypes (genetic variants) correspond to fewer endophenotypes (clusters of symptoms / deficits), all of which might be classified under a single phenotype (diagnostic category).

3.2. Face Tasks in Schizophrenia and Psychosis

Face Tasks (FT) aim to test detection and identification of facial emotional states, which can both affect social cognition. A broad neural network, responsible for social perception, cognition and behaviour has been described, encompassing the amygdalae, the ventromedial prefrontal cortex (VMPFC), the cingulate cortex, somatosensory cortices, the fusiform gyrus and the superior temporal sulcus (STS). Perception of facial emotion, as an essential component of social perception, is mediated by this network [180].

Prosopagnosia, the inability to accurately recognise faces and detect facial emotional states, can be related to occipital lobe pathology, and has been early and broadly encountered in SCZ [181]. SCZ patients have long been recognised as having deficits in emotion processing, which was manifested as dysfunction in the domains of emotional expression, emotional experience (including hedonic responses) and emotional recognition (the ability to accurately identify and interpret emotions from other sources, including facial expressions) [182]; this was attributed to inefficient information processing in a broader neural circuit, including the VMPFC, the cingulate cortex, temporal areas and the amygdala [183]. While healthy controls may activate the amygdala in response to scary / fearful / emotionally charged faces, patients with SCZ may not; on the opposite side a neutral face that will normally induce little activation of the amygdala in a healthy person, can lead to an hyperactivation in a SCZ patient. This may represent a distortion of reality and an inability to interpret social cues, leading to further deficits in judgment and reasoning, or even being linked to more severe psychopathology, such as delusional misidentification [184]. Consequently, negative and affective symptoms of schizophrenia may be linked to reduced emotional processing of positive cues. On the other hand, inappropriate emotional processing of neutral cues could be associated with the development of increased suspiciousness and persecutory beliefs and further lead to impaired interpersonal functioning [185].

3.2.1. Findings from fMRI Studies employing Face Tasks in Schizophrenia

A recent meta-analysis, from year 2012, investigated the amygdala recruitment in SCZ in response to aversive emotional material. *Anticevic et al.* pooled data from 35 trials, employing a variety of face tasks (affect classification / matching / labelling / rating, gender discrimination, mood induction, passive viewing, valence decision / discrimination). They demonstrated that patients with SCZ showed statistically significant, but modest, under-recruitment of bilateral amygdala (mean effect size = -0.20 standard deviations from mean);

however, this effect was dependent on the use of a neutral vs emotion interaction and was not apparent if amygdala activation was evaluated in a negative emotional condition only [40].

Tseng et al., in a more recent meta-analysis, from year 2015, investigated the **multisensory integration** (MSI) in patients with SCZ by gathering data from 29 behavioural and neuroimaging trials. MSI is a spontaneous perceptual-cognitive process by which relevant information from multiple sensory modalities is extracted to generate a holistic experience. The authors concluded that brain functional alterations in the superior temporal cortex and inferior frontal cortex (i.e. attenuated responses during emotionally incongruent stimuli) appear to underlie the deficits in both non-emotional and emotional MSI in schizophrenia patients [186]. These results are in line with the observation made by other authors that ***emotional dysregulation***, *thought to result from a disruption in interactions between prefrontal emotion-controlling regions and subcortical (e.g. amygdala) emotion-generating regions, may be at the core of vulnerability to psychosis* [51].

Several studies using fMRI compared SCZ patients to healthy controls, during a variety of face tasks. A summary of their findings is listed below:

- Unlike controls, SCZ patients have not demonstrated amygdala activation during sad facial stimuli, despite matched ratings to normal controls indicating a similar negative effect [187].
- Positive face discrimination activated the bilateral amygdalae of both controls and SCZ patients, with more prominent activation of the right amygdala shown in the SCZ group. Negative face discrimination activated the bilateral amygdalae in the SCZ group but only the right amygdala in the control group, without any significant group differences [188].
- During a face discrimination and labelling task, controls showed a significantly increased activation of the right middle frontal gyrus with rising task difficulty. SCZ patients demonstrated a significantly decreased activation of the anterior cingulate cortex during facial affect discrimination, a decreased activation of the amygdala-hippocampal complex bilaterally during facial affect labelling and an increased activation of the middle frontal gyrus bilaterally [189].
- During a facial affect and identity discrimination task, SCZ patients failed to activate the right lateral fusiform gyrus, compared to controls [190]; however, during a face identification task, SCZ patients showed the same degree of activation of FFA, compared to healthy controls [191].
- SCZ patients showed reduced limbic activation compared with controls during an emotion identification task. While in controls greater amygdala activation was associated with

correct identifications of anger and fear expressions, SCZ patients showed the opposite effect, portending misidentification [192].

- SCZ patients showed a relative decrease in amygdala activation to fearful faces compared with neutral faces, which resulted from an increase in amygdala activation to the neutral faces, and not from a decreased response to the fearful faces [193].
- Paranoid SCZ patients showed significantly reduced activation in the right amygdala, the right FFA and the left VLPFC, as compared to controls and reduced activation in the left VLPFC as compared to non-paranoid SCZ patients [194].
- During a face encoding task, controls displayed higher activation in the right FFA, more accuracy and shorter reaction times to famous and unfamiliar faces, compared to SCZ patients [195].
- During a gender discrimination task, SCZ patients demonstrated increased FFA activation compared to controls, while processing spatial frequency-degraded faces [196].
- During an emotional valence discrimination task (EVDT) and an age discrimination task (ADT), controls showed activation in the fusiform gyrus, occipital lobe and inferior frontal cortex relative to the resting baseline condition; the increase was greater in the amygdala and hippocampus during the EVDT than during the ADT. In SCZ patients, minimal focal response was observed for all tasks relative to the resting baseline condition [197].

***In summary**, most imaging studies employing face tasks, showed differences in activation between schizophrenia patients and controls in amygdalae, especially with regards to the recognition of angry and fearful faces. Other areas of interest were identified in the VLPFC (including the middle frontal gyri), the anterior cingulate gyri and the FFA. Those differences showed multiple directions; however, schizophrenia patients appear to overall demonstrate decreased activation in the majority of the areas described above.*

An overview of Brodmann Areas (BAs) hosting Regions of Interest (ROIs) showing differences in brain activation between schizophrenia patients and controls, during face tasks, is described in APPENDIX II.

3.3. Reward Tasks in Schizophrenia and Psychosis

Reward tasks target the human brain reward circuit, mediated by a number of mesolimbic structures, including the hypothalamus, the substantia nigra (SN), the nucleus accumbens (NA), the ventral tagmental area (VTA), the amygdala and the hippocampus. Deficits in reward

processing characterize a broad array of neuropsychiatric disorders, including schizophrenia [198].

The most prominent contemporary models of psychosis propose dysfunctional reward processing to be key in the aetiology of the illness [199]. Dopamine dysregulation appears to be the final common pathway to psychosis in schizophrenia; this can alter the appraisal of stimuli, through a process of aberrant salience. The ***aberrant salience model*** proposes the emergence of psychotic symptoms when chaotic dopamine firing attributes significance to irrelevant stimuli (e.g. an aberrant sense of novelty); *hallucinatory experiences* reflect the abnormal salience of the internal representations of perception language and memories; *delusions* are a cognitive scheme that the patient develops to explain aberrant salience experience [200].

Furthermore, *negative symptomatology* in schizophrenia was associated with reduction in ventral striatal activation in anticipation of rewards or punishments [201]. Patients with FEP exhibit abnormal physiological responses associated with reward prediction error in the dopaminergic midbrain, striatum and limbic system and subtle abnormalities to discriminate between motivationally salient and neutral stimuli [202].

*The presence of psychosis symptoms is associated with decreases in striatal activation during **reward tasks** and a reduction in prefrontal cognitive control regions.* However, the frequency and intensity of psychotic symptoms differs from the general population sample through UHR to schizophrenia and the latter is further differentiated by the presence of functional deterioration [203]. Contemporary neuroscience has emphasized the role of PFC in maintaining 'rules' in order to evaluate incoming information as well as internal states to steer responses toward a current goal; If the ***cognitive control hypothesis*** is correct, then one might anticipate that dysfunctional changes in subcortical reward processing in healthy adolescents are compensated for by intact cognitive control mechanisms. A large body of evidence have accounted higher cognitive deficits, seen across the psychosis spectrum, to impaired cognitive control [204].

A combination of aberrant salience and cognitive control hypothesis suggests that the presence of aberrant salience may generate abnormal experiences and these are contextualised appropriately, with no significant functional consequences, if cognitive control mechanisms are operating correctly. This would still result in elevated levels of PLE and possible UHR status, with no transition to psychosis. Failure of the cognitive control mechanisms would however impact on the emergence of clinically relevant symptoms with consequent functional deterioration – and this would be evidenced as psychotic illness.

3.3.1. Findings from fMRI Studies employing Reward Tasks in Schizophrenia

Several studies using fMRI compared schizophrenia patients to healthy controls, during a variety of reward tasks. A summary of their findings is listed below:

- SCZ patients treated with typical (not atypical) antipsychotics showed reduced activation of the ventral striatum (VS) during anticipation of monetary gain, particularly if they reported a high severity of negative symptoms [205].
- Un-medicated SCZ patients showed reduced VS activation during the presentation of reward-indicating cues; this was inversely correlated with the severity of negative (and trend-wise positive) symptoms [206].
- SCZ patients showed inappropriately strong activation in the VS in response to a neutral stimulus in a threatening condition [207].
- Psychotic patients exhibited abnormal physiological responses associated with reward prediction error in the dopaminergic midbrain, striatum, and limbic system [202].
- During reward anticipation, healthy volunteers showed higher VS activation. SCZ patients treated with typical antipsychotics (but not olanzapine), showed decreased left VS activation, which was correlated with negative symptoms [208].
- Un-medicated SCZ patients showed exaggerated activation in the medial PFC as a response to negative outcome in reward trials; in contrast, they showed reduced neural responses to successful versus unsuccessful avoidance of loss in the VS. Increased severity of delusions in schizophrenia patients was associated with a decrease in medial PFC activation elicited by successful versus unsuccessful avoidance of loss [209].
- SCZ patients treated with atypical antipsychotics showed a mesolimbic dopamine hyperactivity and reduced prefrontal activation. During reward expectation, only controls showed increased activation in the anterior cingulate cortex with increasing reward. During outcome, controls showed a U-shaped activation curve in the right VLPFC [210].
- In SCZ patients, VS activation during reward anticipation was negatively correlated with apathy, while receipt of reward was negatively correlated with the severity of depressive symptoms [211].
- In a Monetary Incentive Delay (MID) task, controls but not schizophrenia patients showed greater activation for gains in the medial PFC and the lateral PFC, lateral temporal cortex and amygdalae [212]. Ratings of negative symptoms in SCZ patients correlated with sensitivity to obtained losses in the medial PFC, sensitivity to obtained gains in the lateral PFC, and

sensitivity to anticipated gains in the left VS. Ratings of positive symptoms in SCZ patients also correlated with sensitivity to obtained gains in the lateral PFC.

A recent meta-analysis investigating ventral striatal activation during reward processing in psychosis, pooled data from 23 trials, employing various reward conditions (anticipation, feedback, prediction error) [42]. The authors found significant bilateral VS hypoactivation during reward anticipation in patients compared to healthy controls, which was more severe in subjects with high scores of negative symptoms. Patients also showed hypoactivation during reward feedback.

***In summary**, most imaging studies employing reward tasks, showed differences in activation in schizophrenia patients versus controls in Bilateral VS, the PFC (medial, lateral and VLPFC), the temporal cortices and the anterior cingulate cortices. The nature of these differences varied between studies; however, schizophrenia patients appear to overall demonstrate decreased activation during gain, and reduced discrimination between salient and neutral stimuli.*

An overview of Brodmann Areas (BAs) hosting Regions of Interest (ROIs) showing differences in brain activation between schizophrenia patients and controls, during reward tasks, is described in APPENDIX II.

3.4. The developing brain

Childhood and adolescence are periods or rapid development and critical change for the brain. The neurodevelopmental model of schizophrenia, one of the most widely accepted and prevailing ideas in psychiatry, postulates that the illness is the end of abnormal brain maturation processes, throughout the life span [213]. Knowledge of normal brain development is essential to understanding any abnormal changes leading to the development of psychopathology. This is extremely relevant to my studies, as I am observing a sample of healthy adolescents between the ages of 14 and 19, with focus on individuals with a psychosis proneness phenotype.

A number of studies employing structural MRI have scanned large numbers of children and adolescents repeatedly over time, as the brain develop, tracking volumetric changes in Gray and White Matter (GM, WM) and thus providing a unique developmental perspective on neuropathology [214-218]. Various BAs showed significant structural changes from childhood to adolescence and adulthood, as primarily measured by the ***Distance from Centre*** Difference (DFC) and the ***Gray Matter Density*** (GMD). The DFC measure was developed primarily to measure group differences in local growth. DFC reflects radial expansion measured from the centre of the brain approximately at the midline decussation of the anterior commissure to each of the 65,536 brain surface points. It is of note that the measure at each point for each

individual is reflective of anatomical location in addition to radial expansion; thus, only relative differences in DFC are meaningful in terms of growth [216].

3.4.1. Normal GM Development

The total volume of GM in each lobe and in brain overall, exhibits a pre-pubertal increase, followed by post-pubertal loss. GM volume follows an inverted U-shaped trajectory in frontal, parietal and temporal lobes (FL, PL, TL). The earliest cross-sectional paediatric brain MRI studies of normal developmental changes reported that GM volumes generally declined after 6-7 years of age and continued to decrease during adolescence. Later studies revealed a shifting pattern of GM loss, appearing first (at 4-8 years of age) in dorsal, parietal and primary sensorimotor regions near the interhemispheric margin and spreading laterally and caudally into temporal cortices and anteriorly into dorsolateral and prefrontal cortices. WM volumes increase roughly linearly throughout the first four decades of life, with a peak around the mid-forties when the speed of certain fine motor skills is also optimal [215].

GM development is heterogeneous across the major lobes; FL have peak GM volumes around age 11, while the TL continue to increase in volume until age 14, and the cerebellum show the most protracted developmental time-course. Females achieve peak GM volumes typically 1-2 years earlier than males, particularly for FL, TL and PL [215].

Maturation-related loss of cortical GM density continues over time across the entire age span, with rapid attrition of FL GM in late adolescence. Primary sensorimotor cortices and the frontal and occipital poles mature first, and the remainder of the cortex develops in a parietal to frontal (back-to-front) direction. The superior temporal cortex, which contains association areas that integrate information from several sensory modalities matures last suggesting that the higher-order association areas mature only after the lower-order sensorimotor regions, whose function they integrate, have matured [215]. The first areas to mature are those with the most basic function, such as those processing the senses and movement. Areas involved in spatial orientation and language (parietal lobes) follow, around the ages of puberty (11-13 years). Areas with the most advanced functions – integrating information from the senses, reasoning and other executive functions (e.g. prefrontal cortex) – mature last, in late adolescence. This sequence also provides evidence that phylogenetically older critical areas mature earlier than the more recently evolved higher-order association cortices, which integrate information from earlier maturing cortex [214].

Several studies [216-218] have provided more detailed lists of Brodmann Areas (BAs) with Regions of Interest (ROIs) showing the greatest maturation changes from childhood to adolescent and from adolescence to adulthood. An overview is described in APPENDIX III.

3.4.2. GM Development in Psychosis

Profound and global GM loss with ventricular expansion in seen in Childhood Onset Schizophrenia (COS) [215]; GM loss in COS progressed in a back-to-front (parieto-frontal-temporal) direction during adolescent years. This is strikingly similar to the pattern of GM loss (maturation) seen during normal cortical development, but abnormally accelerated. Profound GM loss in schizophrenia raises a debate about whether this is just a perceived loss resulting from the encroachment of continued white matter growth, a process that normally extends through the fourth decade; in fact, myelination may continue over the entire lifespan, with deteriorative processes beginning to out-weight positive changes by the mid-forties. This process appears to progress in a front-to-back (fronto-parietal) direction and growth rates were correlated with functional prognosis. These findings suggest that the progressive GM deficits seen in schizophrenia are not likely to be the result of WM overgrowth, because WM growth is itself slowed down.

The ***Edinburgh High Risk Study (EHRS)*** have scanned a total of 220 subjects, including 150 UHR individuals for familial reasons, 34 FEP patients and 36 normal controls. Data from the EHRS have revealed changes in GMD in FEP patients and UHR subjects, compared to normal controls:

- Reductions in GMD in FEP patients compared to normal controls in the right anterior cingulate, right medial frontal lobe, left middle temporal gyrus, left post-central gyrus and the left limbic lobe [219].
- Reductions in GMD in UHR subjects compared to controls the in the anterior cingulate and in the left parahippocampal gyrus [220].
- UHR individuals who had transient or isolated psychotic symptoms showed a different spatial pattern of reductions in GMD than those who were free of psychotic symptoms within group comparisons. In addition, those individuals at UHR with transient psychotic symptoms who later developed schizophrenia also showed a different spatial pattern of reduction in GMD in the left temporal lobe and right cerebellum, compared to UHR subjects with transient psychotic symptoms who did not developed schizophrenia [221].
- In UHR subjects, changes over time in the inferior temporal gyrus gave a 60% positive predictive value (likelihood ration >10) of developing schizophrenia to the overall 13% risk in all subjects [222].

***In summary**, the EHRS demonstrated that changes in GMD could be used as part of a predictive test for schizophrenia, in people at enhanced risk for familial reasons. However, due to the limited number of subjects employed in the study, no robust conclusions could be drawn.*

Details are summarized in APPENDIX IV.

3.5. Summary of SCZ cognitive tasks and the developing brain

In studies of face tasks, SCZ patients showed decreased activation compared to controls in the amygdalae, the VLPFC and the FFA, especially during the recognition of angry and fearful faces. In studies of reward tasks, SCZ patients demonstrated decreased activation compared to controls in the VS, the MPFC and the LPFC during gain and reduced discrimination between salient and neutral stimuli.

Profound and global GM loss with ventricular expansion in seen in Childhood Onset SCZ; besides, reductions in GMD have been documented both in FEP patients (in cingulate, frontal and temporal cortices) and UHR subjects (in cingulate and parahippocampal cortices). Changes in GMD could be used as part of a predictive test for psychosis.

Chapter IV: Aim, Materials and Methods

4.1. Aim of the study

In previous chapters I first followed the path of the hunters of biomarkers for psychosis, in the fields of epidemiology, genetics and neuroimaging (chapter I); I examined the literature of PLE, with emphasis on clinical, epidemiological and neuroimaging findings (chapter II, first part); I have then presented the characteristics and previous applications of CAPE, a valid and reliable tool for the assessment of PLE, used in my studies (chapter II, second part). I finally discussed neuroimaging findings from two broadly used cognitive tasks in SCZ, employed in my studies (chapter III, first part) and changes seen in the developing brain from childhood through adolescence to adulthood, to better understand the critical developmental phase my research subjects aged 14 to 19 were going through.

The aim of this study was to examine the neuroimaging profile of healthy adolescents with an increased presence of PLE, representative of the prodromal psychotic phenotype. In the previous chapter, the wealth of data on the deficits in emotional and reward processing seen in patients with psychosis was presented; and how crucial these deficits are considered by contemporary cognitive models on the aetiology of psychosis. A combination of *aberrant salience* (attribution of inappropriate meaning to irrelevant stimuli) with *reduced cognitive control* (which is required to contextualise appropriately these abnormal experiences) *can lead to reality distortion and generate symptoms of psychosis*. Thus, these two cognitive paradigms were employed as avenues to study the neural correlates of PLE. To assess the aberrant salience hypothesis, a ***reward task*** focusing on brain activation during anticipation and feedback of monetary gain was employed; as I have discussed in previous chapters, *the presence of psychosis symptoms was associated with a reduction in striatal activation during reward tasks and a reduction in activation of prefrontal cognitive control regions*. The cognitive control hypothesis was additionally tested by utilising a ***face task*** focusing on brain activation during processing of angry faces; as previously discussed, *emotional dysregulation*, is *thought to result from a disruption in interactions between prefrontal emotion-controlling regions and subcortical (e.g. amygdala) emotion-generating regions*. The dual hypothesis that my group of adolescents with elevated levels of PLE, would present differences in neural activation during a *reward task* and a *face task,* when compared to their counterparts without PLE, was examined. Those differences will be similar to those described in the literature discussed above, listing neural differences between schizophrenia patients and healthy controls, and neural differences between adolescents and young adults with and without prodromal psychotic symptoms.

Hypothesis (Face Task Study)

- Reduced activation of the amygdala and associated network including prefrontal, parahippocampal, insular and caudate regions in high-PLE subjects at age 14 and 19 during a FT [108,51] [see also 3.2.1.].

Hypothesis (Reward Task Study)

- Reduced activation of the prefrontal cortices, the temporal cortices, the cingulate cortices and the striatum in high-PLE subjects at age 14 and 19 during a reward task [102,103] [see also 3.3.1.].

Hypothesis (Neuropsychological Study)

- The presence of increased PLE in adolescence is associated with deficits in performance on risky and affective decision making neuropsychological tasks [104].

4.2. Participants

Neuroimaging and clinical data were obtained from the IMAGEN database, from eight sites in France, Ireland, Germany and the United Kingdom (https://imagen-europe.com/). IMAGEN combines brain imaging, genetics, and psychiatry to increase our understanding of adolescent development and human behaviour such as sensitivity to reward and punishment, impulsivity and emotional response. Research teams from London, Nottingham, Dublin, Paris, Berlin, Hamburg, Mannheim and Dresden have been following 2,000 young people and their parents from the age of 14, with follow up assessments at age 16 and 19. Exclusion criteria encompassed significant pregnancy and birth complications, medical, neurological, psychiatric and neurodevelopmental conditions and MRI contraindications. All local ethics research committees approved the study. Written consent was obtained from the parents or guardians and verbal consent was obtained from the adolescents.

Table 2: IMAGEN Exclusion Criteria

Pregnancy and birth	1. Use of alcohol by the mother during pregnancy (>210 ml alcohol/week)
	2. Diabetes of the mother during pregnancy (onset before pregnancy, treated by insulin)
	3. Premature birth (< 35 weeks) and/or detached placenta
	4. Hyperbilirubinemia requiring transfusion
Medical History	1. Type 1 diabetes
	2. Systemic rheumatological disorders
	3. Malignant tumours requiring chemotherapy
	4. Congenital heart defects or heart surgery
	5. Aneurism
Neurological conditions	1. Epilepsy
	2. Bacterial Infection of CNS
	3. Brain tumour
	4. Head trauma with loss of consciousness >30 minutes
	5. Muscular/myotonic dystrophy

Developmental conditions	1. Nutritional and metabolic diseases
	2. Major neuro-developmental disorders
	3. Hearing deficit requiring hearing aid
	4. Vision problems (strabismus, visual deficit not correctible)
Mental Health	1. Treatment for schizophrenia, bipolar disorder
	2. IQ < 70
MRI Contraindications	1. Metal implants
	2. Electronic implants
	3. Severe claustrophobia

In my study, data from age 14 years as baseline (BL) and age 19 years as follow-up (FU) timepoints were used. A total of 1,434 adolescents were initially selected, based on quality controls and completeness of their behavioural and neuroimaging datasets. The sample was later stratified following 2 distinct methods, as described in the following paragraphs.

4.3. Measures

4.3.1. Psychopathology Measure

At FU assessment, the **Community Assessment of Psychic Experience Questionnaire (CAPE)** was used as a measure of Psychotic-Like Experiences in my adolescent population. The most extended version of CAPE was used, encompassing 42 items, which can be grouped in three dimensions of symptoms: *positive* (comprising bizarre and social delusions), *negative* and *depressive*. Each item is scored based on frequency (how often is the item experienced) and severity (how distressing is the experience):

- Frequency: [0] item is never present; [1] item is sometimes present; [2] item is often present; [3] item is nearly always present
- Severity: [0] item was scored 0 in base of frequency; [1] item is present and not distressing, [2] item is present and a bit distressing; [3] item is present and quite distressing; [4] item is present and very distressing

CAPE-42 worksheet is presented in APPENDIX I; its clustering was already described in **Table 1** (2.2. The Community Assessment of Psychic Experience Questionnaire).

4.3.2. Epidemiological Features

The following parameters were also described in my overall sample (n=1,434): gender (% male); handedness (% right); age at BL and FU; age-normalised IQ at BL; determined by administration of selected subscales of the Wechsler intelligence battery for children (WISC) [223]; estimates of depression as measured by the Adolescent Depression Rating Scale (ADRS) [224]; levels of alcohol consumption, as measured by the Alcohol Use Disorders Identification Test (AUDIT) [225]; levels of cannabis use, as measured by the cannabis scale of the Drug Abuse

Screening Test (DAST) [226]. Verbal IQ was estimated via the vocabulary and similarities subscales; performance IQ was evaluated using the block-design and matrix-reasoning subscales. Correlations between selected CAPE scores and frequencies histograms of those scores are described in APPENDIX VI and APPENDIX VII.

Table 3: Epidemiological Characteristics, Overall Sample

Overall Sample (n=1,434)	Min	Max	Mean	SE	SD	Var
GENDER (Male %)			47.10%			
HANDEDNESS (R %)			86.10%			
AGE BL (y)	12.73	15.92	14.42	0.01	0.40	0.16
AGE FU2 (y)	16.82	22.01	19	0.02	0.76	0.57
WISC VERBAL SCORE (BL)	57	155	112.21	0.41	14.92	222.63
WISC PERFORMANCE SCORE (BL)	63	149	108.65	0.39	14.47	209.39
ADRS TOTAL SCORE (FU)	4	20	18.64	0.06	2.17	4.69
AUDIT TOTAL SCORE (FU)	0	27	5.63	0.11	4.22	17.81
DAST CANNABIS TOTAL SCORE (FU)	0	11	0.89	0.05	1.81	3.29
CAPE GRAND TOTAL SCORE (FU)	0	182	50.21	0.80	30.09	905.20
CAPE POSITIVE Sx TOTAL SCORE (FU)	0	91	13.97	0.29	10.89	118.58
CAPE BIZARRE Sx TOTAL SCORE (FU)	0	60	3.64	0.16	6.01	36.14
CAPE SOCIAL DELUSIONS TOTAL SCORE (FU)	0	41	10.33	0.17	6.44	41.48
CAPE NEGATIVE Sx TOTAL SCORE (FU)	0	74	20.96	0.38	14.22	202.27
CAPE DEPRESSIVE Sx TOTAL SCORE (FU)	0	49	15.28	0.25	9.63	92.76
CAPE ITEMS [5 + 7 + 33] SCORE (FU)	0	16	1.51	0.06	2.34	5.47

Abbreviations
WISC: Wechsler Intelligence Batter for Children [223]; **ADRS:** Adolescent Depression Rating Scale [224]; **AUDIT:** Alcohol Use Disorders Identification Test [225]; **DAST:** Drug Abuse Screening Test [226]; **CAPE:** Community Assessment of Psychic Experiences Questionnaire [73]; **SD:** Standard Deviation; **SE:** Standard Error; **Var:** Variance; **Sx**: Symptoms

4.3.3. CANTAB Measures

Originally developed at the University of Cambridge, the Cambridge Neuropsychological Test Automated Battery (CANTAB) includes highly sensitive, precise and objective measures of cognitive function, correlated to neural networks [227], given the limitations of neuropsychological testing. CANTAB tests have demonstrated sensitivity to detecting changes in neuropsychological performance and include tests of working memory; learning and executive function; visual, verbal and episodic memory; attention, information processing and reaction time; social and emotion recognition, decision making and response control. In my study, the focus was placed on the following CANTAB tasks:

Affective Go-NoGo Task (AGN): assessment of information processing biases for positive and negative stimuli; this task was chosen as a proxy for *'hot' cognition* (cognitive functions mostly influenced by the individual's emotional state), as related to the affective/inhibitory function of frontal and limbic areas of the brain. My rationale for employing this cognitive task is that it rules out a global deficit in cognitive inhibition, in the absence of explicit reward, complementary to my fMRI reward task. Details of AGN task are described in APPENDIX VIII.

Cambridge Guessing Task (CGT): assessment of decision-making and risk-taking behaviour outside a learning context; this task was chosen as a proxy for *'cold' cognition* (cognitive functions mostly independent of the individual's emotional state), as related to the executive functions of the frontal areas of the brain. Details of the CGT task are described in APPENDIX IX.

Participants completed the AGN and CGT tasks both at BL and FU.

4.4. Procedure

4.4.1. Faces Task

In the **Face Task (FT)** volunteers were asked to passively watch short black and white video clips (2-5s) presenting faces with neutral and angry expressions as well as control non-biological motion stimuli (concentric circles). Subjects were shown faces that always started from a neutral expression, and then either turned angry or displayed a neutral movement without a particular emotional content (for example, twitching the nose). These stimuli were arranged in 18s blocks, each block including 4–7 video clips, depicting faces of the same emotion (either angry or neutral). Altogether there were five blocks of neutral faces and five blocks containing angry faces. In between two blocks of face clips, a 18s non-biological control video clip was presented, that consisted of expanding and contracting black-and-white concentric circles of various contrasts, roughly matching the contrast and motion characteristics of video clips. Prior to fMRI scanning, participants were instructed that they would be presented wish short video clips showing faces with angry and neutral expressions as well as moving circles. They were asked to watch the video clips carefully and lie as still as possible during the task. The same instruction was given to them directly before the task started.

Participants completed the FT both at BL and FU. Details of the FT are described in APPENDIX X.

FT includes various contrasts between angry, neutral faces and control stimuli. In my study, I focused on the contrast between angry faces and control stimuli, as this shows maximal effects in the literature and has been described previously [228].

4.4.2. Monetary Incentive Delay Task

The adapted **Monetary Incentive Delay (MID) Task** is a widely-used assessment of rewarded learning ostensibly presented as a reaction time task, testing both motor speed and visual-motor skills by using a monetary incentive. It measures how quickly a subject can react to a briefly presented visual target (the instructions are to press a button with the left or right index finger) that only appears for a short time on the left or right of the screen. If the subject can hit the target, they will score points. The subject can tell where the target will appear and

how many points they can win by the symbol they see on the screen before each trial. A triangle means no points, a circle with a line means 2 points and a circle with three lines means 10 points. Responding too early or too late will result in a loss. The task lasts 11 minutes and is adaptive - the maximum that can be won is 200 points. The subjects receive 1 M&M (or similar chocolates/sweets) for every 5 points to enhance motivation during the task. The MID shows subjects' sequences of clues, target, and feedback phase. The cue indicates the amount of gain and the subjects are instructed to respond when the target shows, roughly 4sec after the clue (anticipation period), after which a 1.5sec feedback message tells the subject about the win or loss of a trial (feedback period).

Participants completed the MID tasks both at BL and FU. Details of the MID task are described in APPENDIX XI.

MID task includes various conditions: reward anticipation and receipt of feedback of positive (small or large win) or negative outcomes (no win). In my study, I focused on the key anticipation and feedback epochs; and the neuroimaging contrast between the large-win and no-win conditions, as these shows maximal effects in the literature and have been described previously [229,230].

4.5. Stratification of the Sample

From the literature [53], two groups in my initial cross sectional assessment were identified: one group with high rates of PLE and the other with low rates of PLE's. I followed a two-step procedure during this stratification process.

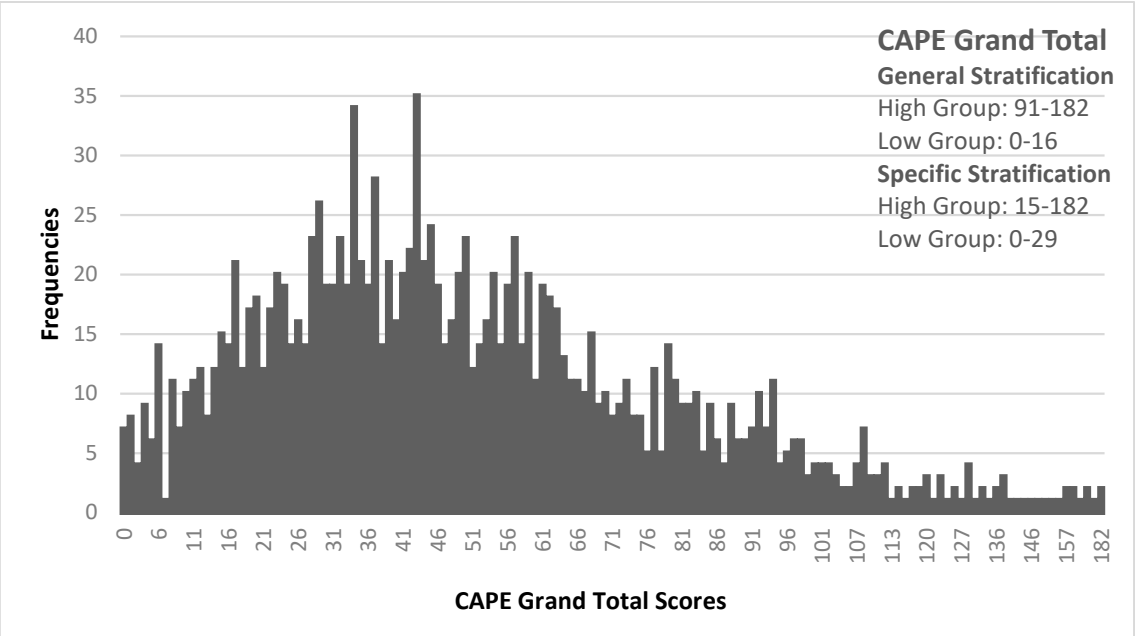
4.5.1. CAPE Total Score, General Stratification

In this approach, high PLE and low PLE group were identified, based on a summary of total scores (frequency and severity) of all 42 items of CAPE. As CAPE total scores did not follow a normal distribution, high and low scorers were selected within the upper and lower 10th percentile. This resulted in n=149 subjects in the high group (representing a psychosis proneness phenotype) and n=149 subjects in the low group (representing healthy controls).

The high group CAPE total score ranged 91-182, corresponding to an itemised score range of 2.17-4.33. As discussed earlier in chapter II, cut-off levels in the area of 2.0 per CAPE item provide adequate positive predictive value for transition to psychosis, based on the relevant literature. The lower edge of my high PLE group range is extremely close to this cut-off values; this provides an extra value of my high PLE group as representative of the psychosis proneness phenotype (see section 2.2.4.). The two groups were equivalent for handedness, age and IQ

scores, with higher percentages of male participants in the low group (56.4% vs 33.6%). The characteristics of both groups are described in detail in APPENDIX XII.

Graph 1: CAPE Grand Total Scores Frequencies Histogram



4.5.2. CAPE 3-Items Score, Specific Stratification

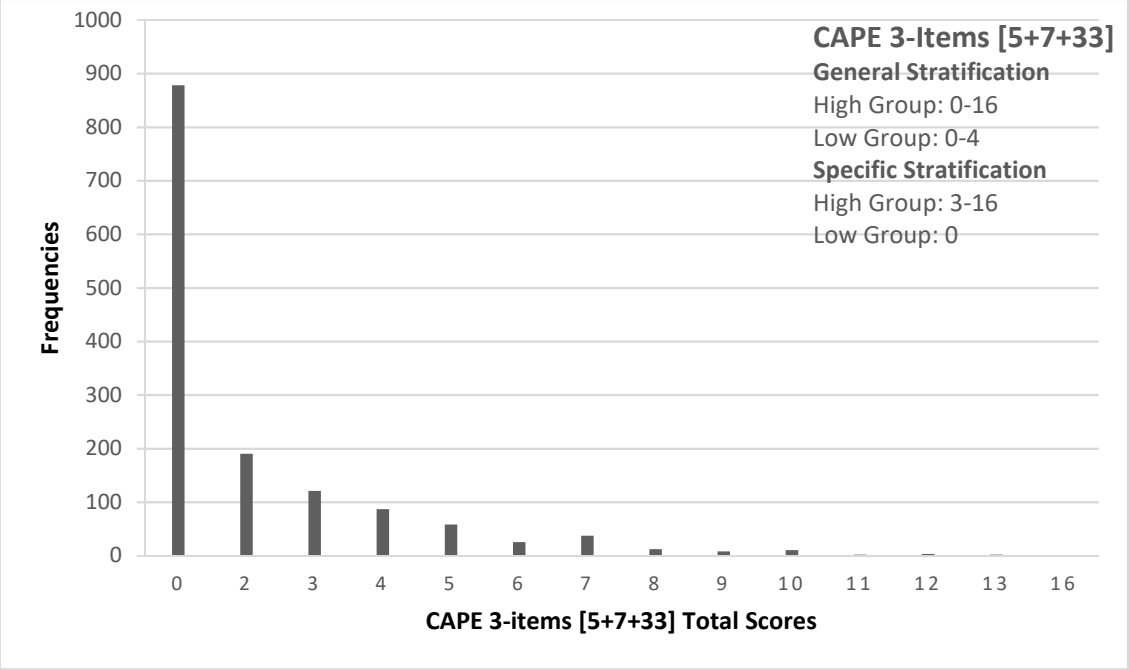
In this approach, focus was placed on specific CAPE items which have a clinical significance and a better predictive value for future transition to psychosis. A study from Australia suggested that *bizarre experiences* and *persecutory ideation* were the subtypes of PLE more strongly associated with distress, depression and poor functioning, which are all risk factors for transition to psychosis [170]. Besides, another study examining the predictive value of adolescent psychopathology, showed that *hallucinations* at age 13 were significantly associated with elevated psychoticism scores (PDI) at age 21 [140]. As discussed earlier, the question about auditory hallucinations (among a 7-item screening questionnaire for PLE) provided the best predictive power for this item and for any PLE [78]. Finally, two studies from Australia [151] and Chile [150], exploring the dimensionality of CAPE-15, revealed a best fit for a hierarchical model, including *persecutory ideation, bizarre experiences and perceptual abnormalities*, as specific factors.

Consequently, 3 representative CAPE items were considered, which could reflect the symptomatology described above. Items *No 5* (*messages from media*, bizarre delusion); *No 7* (*being persecuted*, social delusion) and *No 33* (*auditory hallucinations,* perceptual abnormalities) were chosen and a composite score was generated by adding their total scores (frequency and severity). As my composite scores, did not follow a normal distribution, I selected high and low scorers within the upper and lower 25th percentile, to allow for a greater

variability of the scores within the high group. This resulted in n=366 subjects in the high group (representing a psychosis proneness phenotype) and n=330 subjects in the low group (representing healthy controls).

The high group CAPE 3-items score ranged 3-16, corresponding to an itemised score range of 1-5.33. As discussed earlier in chapter II, cut-off levels in the area of 2.0 per CAPE item provide adequate positive predictive value for transition to psychosis, based on the relevant literature. The lower edge of my high PLE group range is also close to this cut-off values; this provides an extra value of my high PLE group as representative of the psychosis proneness phenotype (see section 2.2.4.). The two groups were equivalent for handedness, age and IQ scores, with higher percentages of male participants in the low group (55.5% vs 41.5%). The characteristics of both groups are described in detail in APPENDIX XIII.

Graph 2: CAPE 3-Items Score Frequencies Histogram



4.6. fMRI Acquisition

Structural and fMRI data were acquired at eight IMAGEN assessment sites with 3-T scanners from various manufacturers (Siemens, Philips, General Electric, and Bruker). The scanning variables were specifically chosen to be compatible with all scanners. The same scanning protocol was used at all sites. In brief, high-resolution T1-weighted three-dimensional structural images were acquired for anatomical localization and co-registration with the functional time series. fMRI blood-oxygen-level-dependent (BOLD) images were acquired with a gradient-echo, echo-planar imaging (EPI) sequence. 191 volumes were acquired for each subject while for the MID task, compared to 202 volumes for the FT Task. Each volume

consisted of 40 slices aligned to the anterior commissure-posterior commissure line (2.4 mm slice thickness, 3.4 mm slice gap) acquired in a descending order. The echo time was optimized (TE=30 ms, TR=2200 ms) to provide reliable imaging of subcortical areas. Voxel size was set at 3.4mm x 3.4mm x 2.4mm, matrix size at 64^2, and FOV at 218mm.

fMRI was performed on 3T scanners from a range of manufacturers (Siemens, Munich, Germany; Philips, Best, The Netherlands; General Electrics, Chalfont St Giles, UK; Bruker, Ettlingen, Germany). A key challenge for the ability to pool data acquired on MR scanners of different manufacturers related to their variation in availability and implementation of particular image-acquisition techniques. To address this problem, for each technique, a set of parameters compatible with all scanners, particularly those directly affecting image contrast or signal-to- noise, was devised and held constant across sites. Where manufacturer-specific choices had to be made (for example the design of head coil), the best manufacturer-specific option was used at all sites with the same scanner type. Two quality control procedures were regularly implemented at each site: (a) The American College of Radiology phantom was scanned to provide information about geometric distortions and signal uniformity related to hardware differences in radiofrequency coils and gradient systems, image contrast and temporal stability, and a custom phantom was scanned for diffusion related parameters. (b) Several healthy volunteers were regularly scanned at each site to assess factors that cannot be measured using phantoms alone and at multiple sites to determine inter-site variability in structural and functional measures (for example, tissue contrast in raw MRI signal, tissue relaxation properties).

A full description of the scanning protocols, their cross-site standardization and quality checks, and pre-processing of resulting data are provided elsewhere [231]; acquisition parameters are summarised in APPENDIX V.

4.7. fMRI Analysis

4.7.1. Pre-Processing

The pre-processing of the EPI data was done with SPM12 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm). Time series data were first corrected for slice-timing, then corrected for movement (spatial realignment), non-linearly warped on the MNI space (using a custom EPI template), and Gaussian-smoothed at 5mm Full Width and Half Maximum (FWHM).

4.7.2. First-Level Analysis

Activation maps were computed with SPM12, and regressed using a general linear model (GLM) with Autoregressive (AR) noise modes (SPM default) against a design-matrix built from

the information contained in the IMAGEN behavioural files. Estimated movement parameters were added to the design matrix in the form of 21 additional columns (3 translations, 3 rotations, 3 translations with a shift x1 TR before, 3 translations shifted x1 TR later and 9 additional columns corresponding to the long-term effects of the movement). The regressors' modelling the experimental conditions were convolved using SPM's default Haemodynamic Response Function (HRF). The estimated model ("beta") parameters maps were linearly-combined to yield contrast maps and significance maps, while the residual variance of the model fit was stored as an additional map.

For the **FT Study**, one within-subject contrast of interest was selected for investigation, both at BL and FU:

- [Angry Faces] – [Control Stimuli].

The selection was made with the intention of exploring inclusively processes relating to brain function in association with emotive/threatening face perception. This approach is advantageous as it permits independent characterisation of the cerebral milieu associated with these conditions, and its results are less dependent on pre-conceived views of the critical distinctions between sub-components of the faces task.

For the **MID Study**, two within-subject contrasts of interest were selected for investigation, both at BL and FU:

- [Anticipation of large win] – [Anticipation of no win].
- [Feedback of large win] – [Feedback of no win].

The selection was made with the intention of exploring processes relating to brain function in association with anticipation and feedback reward processing in general. This approach is advantageous as it permits independent characterisation of the cerebral milieu associated with these conditions, and its results are less dependent on pre-conceived views of the critical distinctions between sub-components of the MDI task.

4.7.3. Second-Level Analysis

As Exploratory whole brain analysis proved insensitive, task-related regions of interest were identified, for the above first-level contrasts, at a corrected Family Wise Error (FEW) of $p<0.05$. *A **functional Regions of Interest (fROI) analysis*** approach was chosen by focusing on high and low CAPE scorers, as described in the stratification of the sample, either using the CAPE total score or the CAPE 3-items score at age 19 years. A mask was applied to identify ROIs at BL and FU based on the four following conditions:

- ROIs showing increased activation in the high PLE group but not the low PLE group ('high>low' or [1 -1])
- ROIs showing increased activation in the low PLE group but not in the high PLE group ('low>high' or [-1 1])
- ROIs showing increased activation both in the high PLE and low PLE groups ('group average positive' or [0.5 0.5])
- ROIs showing decreased activation both in the high PLE and low PLE groups ('group average negative' or [-0.5 -0.5])

This approach provides an unbiased estimate of the activation, as the 'group average positive/negative' are orthogonal to 'high>low' or 'low>high' and is also supported by literature on functional localisers [232]. ROIs were further filtered from supra-threshold based on literature of psychosis and UHR for psychosis, and fewer ROIs were selected for further analysis.

Brain activation levels were extracted for the selected ROIs (expressed as contrast parameter estimates) during the baseline and follow-up states for both stratification approaches. A ***factorial design*** (mixed model 2-way ANOVA with group as fixed and subject as random effects) was employed to investigate the interaction effect of *group*time* and the main effects of *group* (high vs low PLE scorers in both stratification approaches) and *time* (baseline vs follow-up) on brain activation levels, for the ROIs identified previously. Further ***ad-hoc cross-sectional and longitudinal analysis*** was applied to clarify the direction of factorial findings (independent and paired t-tests respectively, at a corrected p=.05 level). ***Additional exploratory analysis*** was also reported, when statistically significant. Effect sizes were calculated and reported.

4.8. CANTAB Measures Analysis

The following **measures**, from the AGN and CGT tasks, were included in my analysis.

- ***AGN Total Omissions Negative/Positive:*** total number of missed responses to targets in the blocks specified by the value of target type (negative, positive).
- ***CGT Risk Adjustment*****:** Participants are expected to gamble an increased amount of their points when the odds are in their favour. Specifically, higher bets should be evident when the majority of the boxes are that of the colour chosen. Risk adjustment measures the tendency to gamble higher proportions of points on trials where a larger proportion of the boxes are of the participant's chosen colours.

A ***factorial design*** (mixed model 2-way ANOVA with group as fixed and subject as random effects) was employed to investigate the interaction effect of *group*time* and the main effects of *group* (high vs low PLE scorers in both stratification approaches) and *time* (baseline vs follow-up) on AGN and CGT scores. Further ad-hoc cross-sectional and longitudinal analysis was applied to clarify the direction of factorial findings (independent and paired t-tests respectively, at a corrected p=.05 level). Effect sizes were calculated and reported.

Chapter V: The Faces Task Study

5.1. Overview

Objective

To examine the neuroimaging profile of healthy adolescents with an increased presence of Psychotic-Like Experiences (PLE), during a face cognitive task.

Method

1,434 adolescents were assessed at 2 timepoints using functional MRI during a Faces Task (FT) at age 14 and 19 years. The sample was stratified into two groups of high PLE and low PLE based on their scores on the CAPE-42 questionnaire at age 19. A general and specific stratification was applied, the general stratification used the CAPE Total Score, while the specific stratification used a CAPE Score of 3 specific clinically significant items. The first level analysis focused on a pre-defined contrast of [Angry Faces] – [Control Stimuli]. The second level analysis examined between-group differences using an a priori defined region of interest approach (ROIs). I performed a factorial analysis to examine the main effects of *group*, *time* and their interaction on brain activation. Additionally, I performed an exploratory analysis, by employing both a cross-sectional design to compare brain activation levels between the high PLE and low PLE groups at ages 14 and 19, and a longitudinal design to compare brain activation levels between the two timepoints.

5.2. Results of fMRI Analysis

The following ROIs were initially identified through the literature of faces, emotion and social cognition processing in psychosis and UHR for psychosis [51,194] and filtered through the second-level analysis. The ROIs listed here [MNI coordinates] showed differences in brain activation between groups (high PLE vs low PLE) and timepoints (BL vs FU). The main effect of *group, time* and the interaction of *group*time* on brain activation levels was examined by employing a mixed model 2-way ANOVA, and post-hoc paired/independent T-tests.

General Stratification ROIs

[42 8 -14] Right Insular Cortex, BA13 (BL)

[-12 5 10] Left Caudate Body (FU)

[6 65 31] Right Frontal Lobe, Superior Frontal Gyrus, BA10 (FU)

[33 -46 -5] Right Limbic Cortex, Parahippocampal Gyrus, BA19 (FU)

Specific Stratification ROIs

[-6 -73 -26] Left Cerebellum, Posterior Lobe, Declive (BL)

[-33 11 10] Left Insular Cortex, BA13 (BL)

[-15 -40 -44] Left Cerebellum, Posterior Lobe, Tonsil (FU)

[-33 17 -11] Left Insular Cortex, BA13 (FU)

5.2.1. Retrospective Control for Multiple Testing

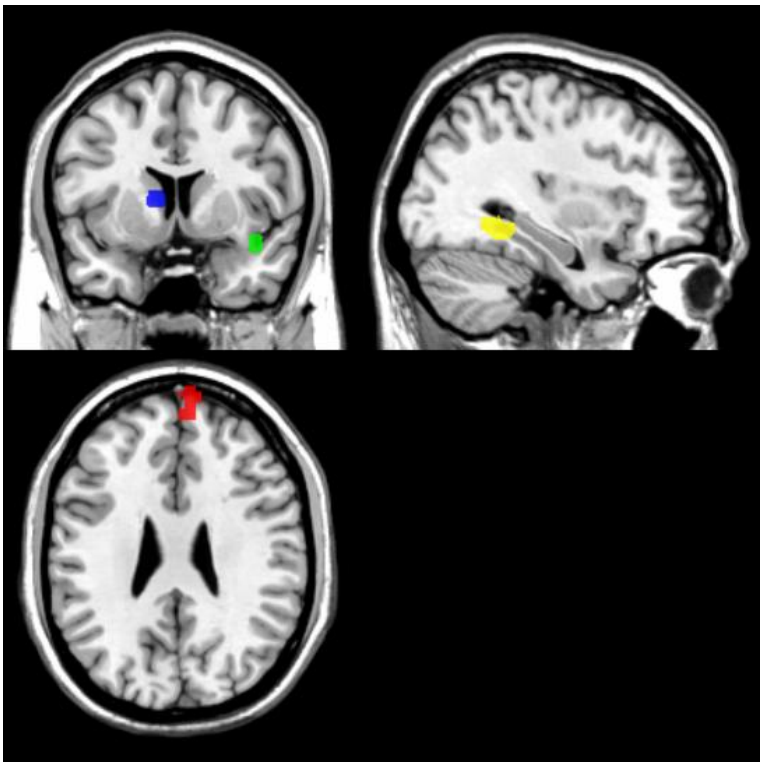
As multiple ROIs resulted from my Analysis, I performed a retrospective correction of the statistical significance threshold of the whole brain analysis, at a contrast level. As eight ROIs were identified in the [angry – control] contrast, I used a Bonferoni correction, introducing a new level of statistical significance at 0.00625 (0.05 / 8). Acknowledging this approach is a rather conservative one, I chose to present all eight ROIs, noting however that [42 8 -14] and [-33 17 -11] did not survive the updated threshold of 0.00625, corrected for multiple testing.

5.2.2. General Stratification

Figure 2: FT Study, ROIs selected for Analysis, General Stratification

BASELINE
[42 8 -14]: Right Insular Cortex
(H>L)

FOLLOW-UP
[-12 5 10]: Left Caudate Body
(L>H)
[6 65 31]: Right Superior Frontal Gyrus
(L>H)
[33 -46 -5]: Right Parahippocampal Gyrus
(L>H)



For more detailed illustrations see APPENDIX XXI: General Stratification

Right Insular Cortex [42 8 -14]

There was an interaction effect of *group*time* [*F*(1, 230)=7.4, p=0.007], which was driven by a differential change in brain activation from *BL to FU,* showing significant *increase* in the low PLE group (t=-2.0, p=0.043), and non-significant decrease in the high PLE group. Additional exploratory analysis exhibited higher brain activation of the high PLE group compared to the low PLE group at *BL* (t=5.2, p<0.0001).

Left Caudate Body [-12 5 10]

No effects of *group*time*, *group* nor *time* were reported. Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group *at FU* (t=-2.588, p=0.01).

Right Superior Frontal Gyrus [6 65 31]

There was a main effect of *group* [*F*(1, 230)=4.2, p=0.041], which was driven by higher brain activation of the low PLE group compared to the high PLE group *at FU* (t=-2.3, p=0.023). There was a main effect of *time* [*F*(1, 230)=6.9, p=0.009], which was driven by an *increase* in brain activation from *BL to FU*, significant only for the low PLE group, (t=-3.3, p=0.001).

Right Parahippocampal Gyrus [33 -46 -5]

There was a main effect of group [*F*(1, 230)=4.9, p=0.028], which was driven by higher brain activation of the low PLE group compared to the high PLE group *at FU* (t=-2.8, p=0.005). There was a main effect of time [*F*(1, 230)=12.1, p=0.001], which was driven by a *decrease* in brain activation from *BL to FU*, significant only the high PLE group (t=4.3, p<0.0001).

Table 4: FT Study, Factorial Analysis, Mixed Model 2-Way ANOVA, General Stratification

	Type III Sum of Squares	df	Mean Square	F	Sig.	r
Insular ROI [42 8 -14] Brain Activation, General Stratification						
GROUP	3.921	1	3.921	19.522	<0.0001	0.280
TIME	0.002	1	0.002	0.002	0.968*	0.003
GROUP * TIME	8.229	1	8.229	7.458	0.007	0.177
Error(GROUP)	46.196	230	0.201			
Error(TIME)	253.769	230	1.103			
Caudate ROI [-12 5 10] Brain Activation, General Stratification						
GROUP	0.185	1	0.185	3.036	0.083*	0.114
TIME	0.393	1	0.393	1.711	0.192*	0.086
GROUP * TIME	0.734	1	0.734	3.200	0.075*	0.117
Error(GROUP)	13.987	230	0.061			
Error(TIME)	52.784	230	0.229			
Frontal ROI [6 65 31] Brain Activation, General Stratification						
GROUP	1.146	1	1.146	4.212	0.041	0.134
TIME	4.827	1	4.827	6.978	0.009	0.172
GROUP * TIME	2.195	1	2.195	3.174	0.076*	0.117
Error(GROUP)	62.564	230	0.272			
Error(TIME)	159.102	230	0.692			
Limbic ROI [33 -46 -5] Brain Activation, General Stratification						
GROUP	0.455	1	0.455	4.899	0.028	0.144
TIME	3.171	1	3.171	12.106	0.001	0.224
GROUP * TIME	0.723	1	0.723	2.76	0.098*	0.109
Error(GROUP)	21.358	230	0.093			
Error(TIME)	60.247	230	0.262			

Abbreviations
df: degrees of Freedom; **F:** F-ratio; **(*)**: not statistically significant at a p=0.05 level;
r: Pearson's correlation coefficient;

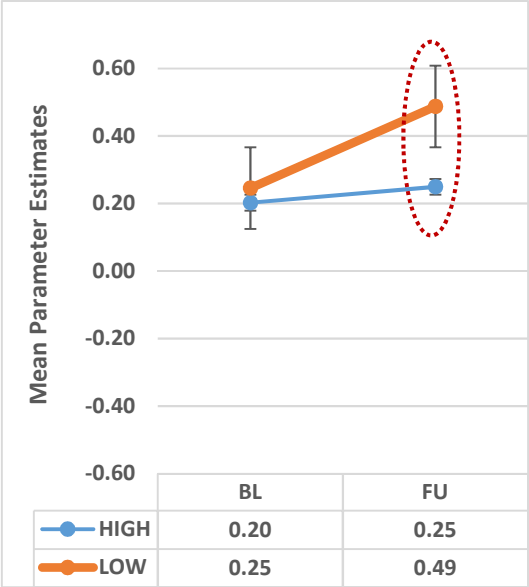
For a table of fROIs brain analysis results see APPENDIX XIV: General Stratification

For a table of cross-sectional analysis results see APPENDIX XV: General Stratification

For a table of longitudinal analysis results see APPENDIX XVI: General Stratification

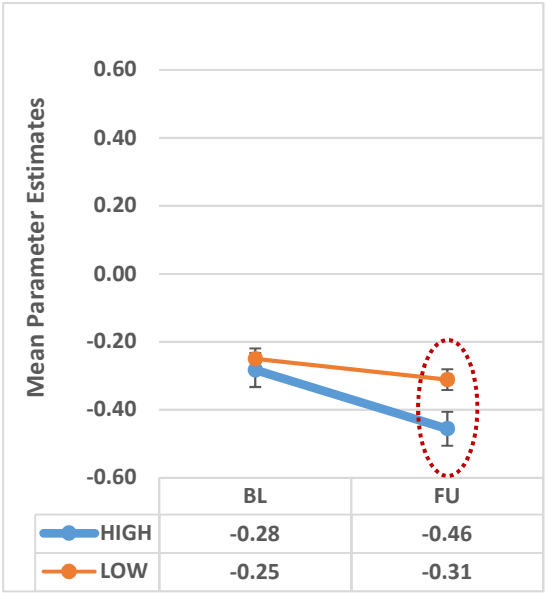
Graph 3: FT Study, Longitudinal Analysis Graphs, General Stratification

Brain Activation at BL and FU, ROI [6 65 31], Right Superior Frontal Gyrus



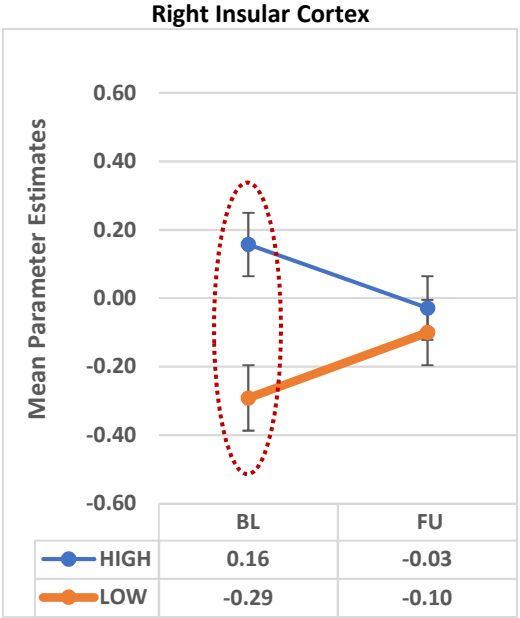
Longitudinal changes are statistically significant (p<.05) for the **Low PLE Group** only (thick line); **encircled** (red dotted line) are statistically significant cross-sectional differences (p<.05); SE bars are displayed.

Brain Activation at BL and FU, ROI [33 -46 -5], Right Parahippocampal Gyrus



Longitudinal changes are statistically significant (p<.05) for the **High PLE Group** only (thick line); **encircled** (red dotted line) are statistically significant cross-sectional differences (p<.05); SE bars are displayed.

Brain Activation at BL and FU, ROI [42 8 -14], Right Insular Cortex



Longitudinal changes are statistically significant (p<.05) for the **Low PLE Group** only (thick line); **encircled** (red dotted line) are statistically significant cross-sectional differences (p<.05); SE bars are displayed.

Table 5: FT Studies, Summary of Findings, General Stratification

Brain ROI	Factorial Analysis (sign. effects)	Exploratory Analysis		
		BL state	BL to FU changes	FU state
Right Insular Cortex **[42 8 -14]**	**Group*Time**	**H>L**	**H** ↓ NS **L** ↑	
Left Caudate Body **[-12 5 10]**				**L>H**
Right Superior Frontal Gyrus **[6 65 31]**	**Group** **Time**		**H** ↑ NS **L** ↑	**L>H**
Right Limbic Cortex **[33 -46 -5]**	**Group** **Time**		**H** ↓ **L** ↓ NS	**L>H**

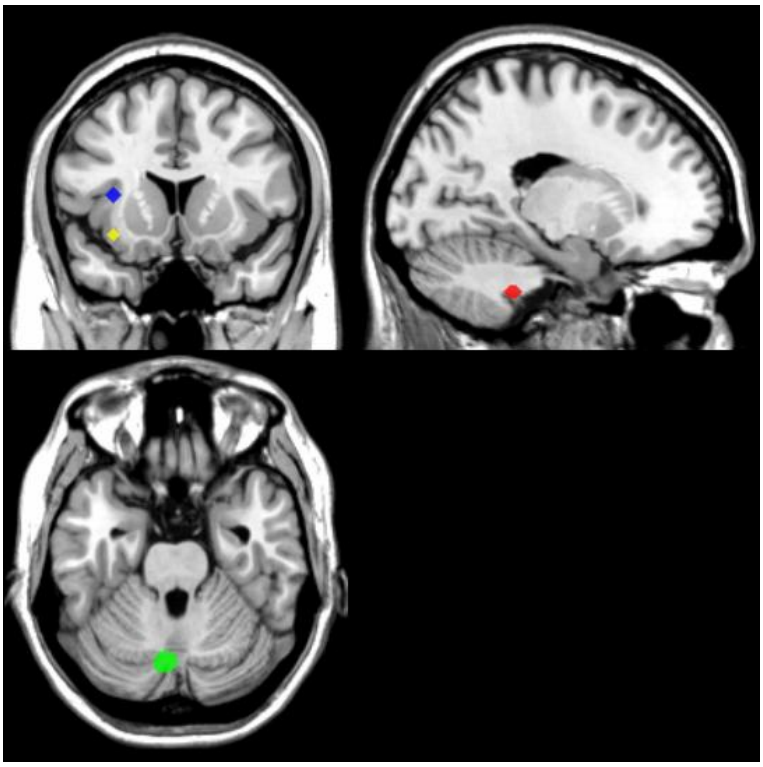
H: High PLE Group; **L**: Low PLE Group;
↑: Increase in brain activation (statistically significant);
↑ NS: Increase in brain activation (statistically non-significant);
↓: Decrease in brain activation (statistically significant);
↓ NS: Decrease in brain activation (statistically non-significant)

5.2.3. Specific Stratification

Figure 3: FT Study, ROIs selected for Analysis, Specific Stratification

BASELINE
[-6 -73 -26]: Left Cerebellar Declive
(H>L)
[-33 11 10]: Left Insular Cortex
(L>H)

FOLLOW-UP
[-15 -40 -44]: Left Cerebellar Tonsil
(L>H)
[-33 17 -11]: Left Insular Cortex
(L>H)



For more detailed illustrations see APPENDIX XXII: Specific Stratification

Left Cerebellar Declive [-6 -73 -26]

There was a main effect of group [*F*(1, 549)=7.196, p=0.008], which was driven by higher brain activation of the high PLE group compared to the low PLE group *at BL* (t=2.828, p=0.005).

Left Insular Cortex [-33 11 10]

There was an interaction effect of *group*time* [*F*(1, 549)=11; p=0.001], which was driven by a differential change in brain activation from *BL to FU*, showing significant *decrease* in the low PLE group (t=3.38, p=0.001) and non-significant increase in the high PLE group. Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group at *BL* (t=-2.278, p=0.023).

Left Cerebellar Tonsil [-15 -40 -44]

No effects of *group*time*, *group* nor *time* were reported. Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group at *FU* (t=-2.75, p=0.006).

Left Insular Cortex [-33 17 -11]

There was a main effect of *group* [*F*(1, 549)=5.228, p=0.023], which was driven by higher brain activation of the low PLE group compared to the high PLE group at *FU* (t=-2.275, p=0.023).

There was a main effect of time [*F*(1, 549)=7.336, p=0.007], which was driven by a *decrease* in brain activation from *BL to FU*, significant only for the low PLE group (t=3.258, p=0.001).

Table 6: FT Study, Factorial Analysis, Mixed Model 2-Way ANOVA, Specific Stratification

	Type III Sum of Squares	df	Mean Square	F	Sig.	r
Cerebellar ROI [-6 -73 -26] Brain Activation, Specific Stratification						
GROUP	0.591	1	0.591	7.196	0.008	0.114
TIME	0.755	1	0.755	3.201	0.074*	0.076
GROUP * TIME	0.595	1	0.595	2.525	0.113*	0.068
Error(GROUP)	45.060	549	0.082			
Error(TIME)	129.414	549	0.236			
Insular ROI [-33 11 10] Brain Activation, Specific Stratification						
GROUP	0.012	1	0.012	0.133	0.715*	0.016
TIME	1.092	1	1.092	3.679	0.056*	0.082
GROUP * TIME	3.263	1	3.263	11	0.001	0.140
Error(GROUP)	47.887	549	0.087			
Error(TIME)	162.872	549	0.297			
Cerebellar ROI [-15 -40 -44] Brain Activation, Specific Stratification						
GROUP	0.001	1	0.001	0.017	0.896*	0.006
TIME	0.175	1	0.175	1.005	0.317*	0.043
GROUP * TIME	0.015	1	0.015	0.087	0.768*	0.013
Error(GROUP)	95.561	549	0.174			
Error(TIME)	95.561	549	0.174			
Insular ROI [-33 17 -11] Brain Activation, Specific Stratification						
GROUP	0.53	1	0.53	5.228	0.023	0.097
TIME	2.217	1	2.217	7.336	0.007	0.115
GROUP * TIME	1.003	1	1.003	3.32	0.069*	0.078
Error(GROUP)	55.619	549	0.101			
Error(TIME)	165.894	549	0.302			

Abbreviations
df: degrees of Freedom; **F:** F-ratio; **(*)**: not statistically significant at a p=0.05 level;
r: Pearson's correlation coefficient;

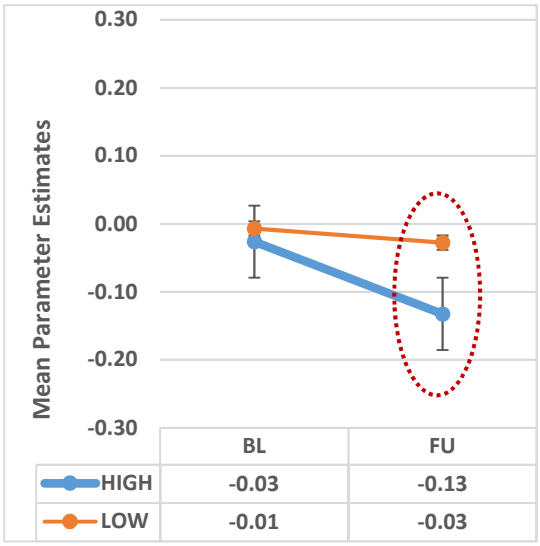
For a table of fROIs brain analysis results see APPENDIX XIV: Specific Stratification

For a table of cross-sectional analysis results see APPENDIX XV: Specific Stratification

For a table of longitudinal analysis results see APPENDIX XVI: Specific Stratification

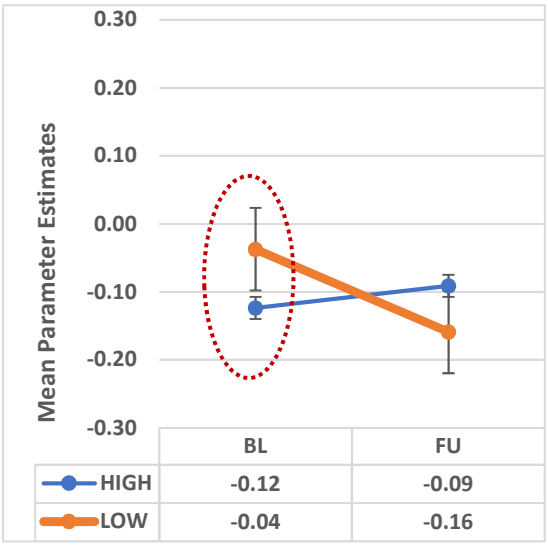
Graph 4: FT Study, Longitudinal Analysis Graphs, Specific Stratification

Brain Activation at BL and FU, ROI [-33 17 -11], Left Insular Cortex



Longitudinal changes are statistically significant (p<.05) for the **High PLE Group** only (thick line); **encircled** (red dotted line) are statistically significant cross-sectional differences (p<.05); SE bars are displayed.

Brain Activation at BL and FU, ROI [-33 11 10], Left Insular Cortex



Longitudinal changes are statistically significant (p<.05) for the **Low PLE Group** only (thick line); **encircled** (red dotted line) are statistically significant cross-sectional differences (p<.05); SE bars are displayed.

Table 7: FT Study, Summary of Findings, Specific Stratification

Brain ROI	Factorial Analysis (sign. effects)	Exploratory Analysis		
		BL state	BL to FU changes	FU state
Left Cerebellum **[-6 -73 -26]**	**Group**	**H>L**		
Left Insular Cortex **[-33 11 10]**	**Group*Time**	**L>H**	**H** ↑ NS **L** ↓	
Left Cerebellum **[-15 -40 -44]**				**L>H**
Left Insular Cortex **[-33 17 -11]**	**Group** **Time**		**H** ↓ **L** ↓ NS	**L>H**

H: High PLE Group; **L**: Low PLE Group;
↑: Increase in brain activation (statistically significant);
↑ NS: Increase in brain activation (statistically non-significant);
↓: Decrease in brain activation (statistically significant);
↓ NS: Decrease in brain activation (statistically non-significant);

5.3. Results of CANTAB Measures

The main effect of *group, time* and the interaction of *group*time* on CANTAB measures was examined by employing a mixed model 2-way ANOVA, and post-hoc paired/independent T-tests.

Table 8: CANTAB Measures Factorial Analysis, Mixed Model 2-Way ANOVA, General & Specific Stratification

	Type III Sum of Squares	df	Mean Square	F	Sig.	r
AGN Total Omissions Negative Scores, General Stratification						
GROUP	73.817	1	73.817	2.498	.116*	0.124
TIME	3006.213	1	3006.213	50.236	<0.0001	0.490
GROUP * TIME	144.599	1	144.599	2.416	.122*	0.122
Error(GROUP)	4699.301	159	29.555			
Error(TIME)	9514.780	159	59.841			
AGN Total Omissions Positive Scores, General Stratification						
GROUP	77.094	1	77.094	2.919	.089*	0.134
TIME	3423.720	1	3423.720	58.778	<0.0001	0.520
GROUP * TIME	77.335	1	77.335	1.328	.251*	0.091
Error(GROUP)	4199.102	159	26.409			
Error(TIME)	9261.485	159	58.248			
CGT Risk Adjustment Scores, Specific Stratification						
GROUP	2.360	1	2.360	3.143	.077*	0.076
TIME	53.065	1	53.065	52.930	<0.0001	0.298
GROUP * TIME	8.273	1	8.273	8.252	.004	0.122
Error(GROUP)	406.935	542	.751			
Error(TIME)	543.379	542	1.003			

Abbreviations
df: degrees of Freedom; **F:** F-ratio; **(*)**: not statistically significant at a p=0.05 level; **r:** Pearson's correlation coefficient;

For a table of cross-sectional analysis results see APPENDIX XX: Cross-Sectional Analysis

For a table of longitudinal analysis result see APPENDIX XX: Longitudinal Analysis

5.3.1. General Stratification

There was a main effect of *time* on AGN Total Omissions for both positive [$F(1, 159)=58.8$, $p<0.0001$] and negative stimuli [$F(1, 159)=50.2$, $p<0.0001$], which was driven by a *decrease from BL to FU*, across the high PLE group (AGN positive: $t=4.5$, $p<0.0001$; AGN negative: $t=3.7$, $p<0.001$) and the low PLE group (AGN positive: $t=6.3$, $p<0.0001$; AGN negative: $t=6.4$, $p<0.0001$). Additional exploratory analysis revealed that the high PLE group scored lower compared to the low PLE group on AGN Total Omissions for both positive and negative stimuli *at BL*.

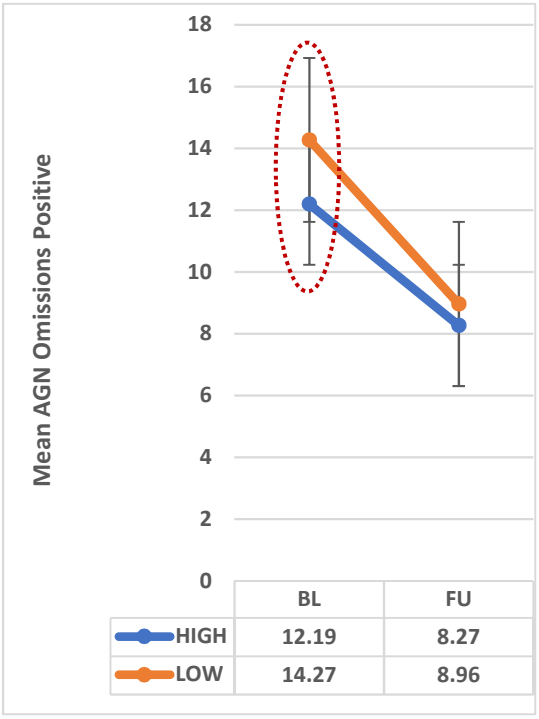
5.3.2. Specific Stratification

There was an interaction effect of *group*time* on CGT Risk Adjustment scores [$F(1, 542)=8.252$, $p=0.004$], which was driven by an *increase from BL to FU,* significant for both the high PLE

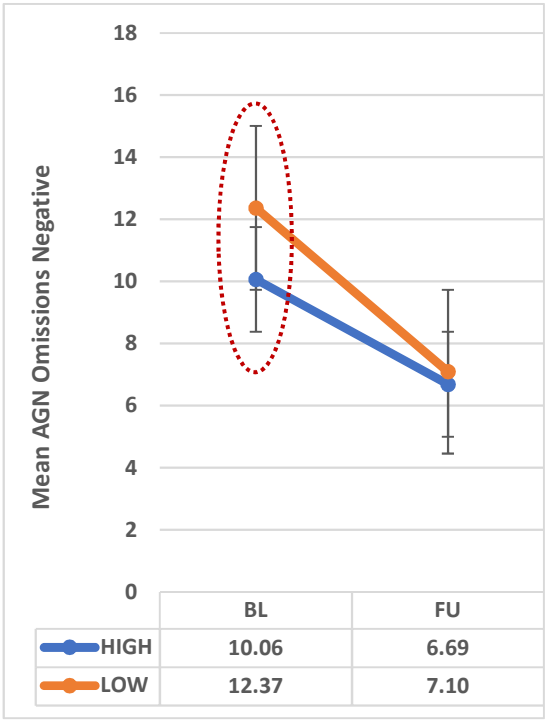
group (t=-7.313, p<0.0001) and the low PLE group (t=-3.058, p<0.0001); the high PLE group showed however a steeper increase between BL and FU, compared to the low PLE group.

Graph 5: CANTAB Measures, Longitudinal Analysis Graphs, General & Specific Stratification

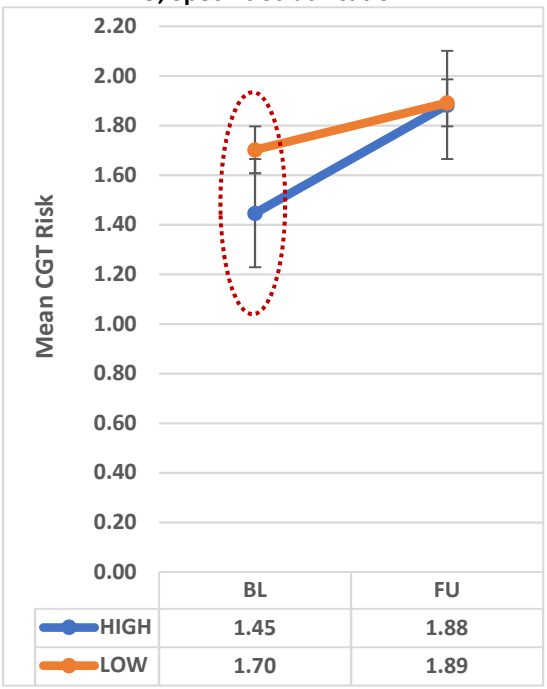
AGN Total Omissions Positive Stimuli Mean Scores at BL and FU, General Stratification



AGN Total Omissions Negative Stimuli Mean Scores at BL and FU, General Stratification



CGT Risk Adjustment Mean Scores at BL and FU, Specific Stratification



Longitudinal changes are statistically significant (p<.05) for the **High PLE Group** and the **Low PLE Group** (thick lines); **encircled** (red dotted line) are statistically significant cross-sectional differences (p<.05); SE bars are displayed.

5.4. Correlations

In exploratory analysis, I investigated whether brain activation levels for my identified fROIs correlated with selected CAPE and CANTAB scores. The strength of these correlations proved weak, though numerous statistically significant results were generated. Most notably, baseline BOLD signals of the Right Insular ROI [42 8 -14] positively correlated with CAPE grand total scores (rho=0.292, p<0.0001) and CAPE 3-items scores (rho=0.265, p<0.0001);

See Appendix XXV

Table 9: CANTAB Measures, Summary of Findings, General & Specific Stratification

CANTAB score	Stratification	Factorial Analysis (sign. effects)	Exploratory Analysis		
			BL state	BL to FU changes	FU state
AGN Total Omissions, Positive Stimuli	General	**Time**	**L>H**	**H ↓** **L ↓**	
AGN Total Omissions, Negative Stimuli	General	**Time**	**L>H**	**H ↓** **L ↓**	
CGT Risk Adjustment	Specific	**Group*Time**	**L>H**	**H ↑** **L ↑**	

H: High PLE Group; **L**: Low PLE Group;
↑: Increase in CANTAB score (statistically significant);
↓: Decrease in CANTAB score (statistically significant)

5.5. Discussion

5.5.1. Overview of fMRI Studies

The primary finding, if one looks at ROIs based on the general PLE stratification, is that brain areas showed differences in brain activation at BL and FU, between the high PLE and low PLE groups. *In summary,* in the high PLE group, an early state of hyperactivation in right insular cortical areas [42 8 -14], was replaced by a later state of hypoactivation in right frontal [6 65 31] limbic [33 -46 -5] and left striatal [-12 5 10] areas, when the general stratification was applied.

Secondary findings, if one looks at ROIs based on the specific stratification, are that *similar* brain areas showed differences in brain activation at both BL and FU, between the high PLE and low PLE groups. *In summary,* in the high PLE group, an early state of hyperactivation in a left cerebellar area [-6 -73 -26] and hypoactivation in a left insular area [-33 11 10], was replaced by a later state of hypoactivation in both a left cerebellar area [-15 -40 -44] and a left insular area [-33 17 -11], when the specific stratification was applied.

My longitudinal studies revealed differences in brain activation between BL and FU in relatively fewer brain areas, compared to the ones identified in the cross-sectional studies. *In summary,* in the high PLE group, there was a decrease in brain activation between BL and FU in a right limbic area and a left insular area.

My results nevertheless provide a partial confirmation of my research hypothesis, as engagement of prefrontal, parahippocampal, insular and caudate areas (but not the amygdala) was reaffirmed.

5.5.2. Interpretation of fMRI Results

Adolescents with high levels of PLE were examined using fMRI during facial emotions task. Under a wider consideration, identified ROIs appear connected to a broader neural circuit responsible for integrating social perception, cognition and behaviour, as was described earlier [180]. Dysregulation of this circuit leads to deficits in social perception, cognition and behaviour. Misidentification of facial expressions represent a crucial deficit during this process, and as observed extensively in SCZ literature, it can give rise to impaired social interactions and the development of paranoia.

From a different perspective, young people at UHR of psychosis exhibit HPA axis hyper-activation and higher levels of plasma cortisol, which were positively associated with levels of depression and anxiety [233]; the ***stress-vulnerability model*** has been already proposed for the aetiology of SCZ [234]. One could hypothesize that abnormal facial processing, can both invoke

and amplify stress reactions; amygdala and the prefrontal cortex are indeed components of both the 'social' and 'stress' systems of the brain.

Considering my high PLE group results from a neuro-developmental point of view one needs to distinguish between ***states*** (patterns of brain activation which are pertinent only to a particular timepoint) versus ***traits*** (patterns of brain activation which persist along various timepoints).

In my cross-sectional studies, I revealed different hypoactivation and hyperactivation ***states*** at different timepoints, with relatively more brain areas involved at FU compared to BL, when I consider a general stratification of my sample. These observations might represent a developmental process in the course of the prodromal psychosis phenotype, during which fewer areas show aberrant activation at BL (insular cortex, cerebellum), compared to FU (frontal, limbic, insular, caudate and cerebellum). My longitudinal studies confirmed that in the high PLE group, brain activation of a limbic area [33 -46 -5], showed a significant decrease between BL and FU; the same area was also hypoactive at FU in the high PLE group. This variation could potentially underpin an ***'aberrant' developmental process***, leading to under-recruitment of critical limbic areas during perception of angry faces, generating its full potential at a later age and, thus introducing a risk for the future emergence of psychosis. Similarly, in the high PLE group, brain activation of a frontal area [6 65 31] showed a non-significant increase between BL and FU; the same area remained hypoactive at FU in the high PLE group, compared to the low PLE group, which could also represent a ***stable deficit*** in frontal activation. The above changes followed similar directions in both groups; however, an insular area [42 8 -14] exhibited opposing trends in brain activation changes between BL and FU (non-significant decrease in the high PLE group vs significant increase in the low PLE group). The significance of this finding is not clear; it is possible however that this area of maximum divergence can have a role in differentiating the two groups, during a facial-emotional task.

Hypoactivation of ***frontal areas*** might also represent a ***trait*** in the development of psychosis, as it appears in all phases of the continuum, from prodromal to schizophrenia. Frontal hypoactivation or ***'hypo-frontality'*** has been extensively researched in schizophrenia, in relation to a variety of behaviours, including motivation, executive functions and psychotic symptomatology [235]. Another position is that during working memory tasks, patients with schizophrenia can either recruit more extended prefrontal resources, or fail to sustain recruitment of adequate prefrontal areas, compared to controls, which eventually results in poorer outcomes [236]. Besides, functional ***dysconnectivity of fronto-striatal circuitry*** can represent a risk phenotype for psychosis. First-episode psychosis is associated with pronounced dysregulation of cortico-striatal systems, characterized most prominently by

hypo-connectivity of dorsal and hyper-connectivity of ventral fronto-striatal circuits [237]. A meta-analysis of neurofunctional correlates of vulnerability to psychosis revealed hypoactivation of DLPFC and VLPFC as the most common finding in UHR and FEP populations [238]. Even in healthy individuals, aberrant front-striatal prediction error signal, during a causal learning task, correlate with the severity of their delusion-like beliefs [239]. In my cross-sectional study, when the general stratification was applied, I noted hypoactivation of a frontal [6 65 31] and a striatal [-12 5 10] area in the high PLE group at FU, a finding consistent with perturbed fronto-striatal connectivity.

Additionally, when I consider a specific stratification of my sample, hypoactivation of two insular areas might also represent a ***trait*** across my two timepoints; the same applies to the cerebellum, where hyperactivation at an early phase is followed by hypoactivation at a later phase. Evidence suggest that ***cerebellum*** plays a role in cognition in healthy humans, and that cerebellar abnormalities occur in schizophrenia [240]. Andreasen and colleagues proposed a model that implicated connectivity among nodes located in prefrontal regions, the thalamic nuclei and the cerebellum [241]. A disruption in this circuitry produces ***'cognitive dysmetria'***, which manifests as difficulty in prioritising, processing, coordinating and responding to information. This 'poor mental coordination' is a fundamental cognitive deficit in schizophrenia and can account for its broad diversity of symptoms. Consequently, my finding of BL hyperactivation and FU hypoactivation in two cerebellar ROIs in the high PLE group might represent an early indication of a pathology that could later generate a more pronounced deficit.

A notable observation is the lack of ***amygdala*** regions among my results. Aberrant activation of the amygdala during a face recognition is probably one of neuroimaging hallmarks of psychosis. A study employing a similar IMAGEN sample as ours revealed that subjects with PLE demonstrated, among other findings, *increased* hippocampus/amygdala activation during processing of neutral faces, compared to controls [108]. It is of note however, that the authors of this study employed a smaller sample (n=27), assessed PLEs at age 14 only and used a less extended assessment tool focusing on perceptual abnormalities and delusional thoughts. Besides, it is important to note that I am assessing a non-clinical group of subjects; thus, my findings might correspond to prodromal brain alterations in a trajectory toward psychosis and predate changes that are later seen more consistently across the psychosis continuum.

The ***schizophrenia literature*** of neuroimaging studies involving face tasks, has revealed a multitude of ROIs in various Broadmann Areas (BAs), with differences in brain activation between patients with schizophrenia or first-episode psychosis and healthy controls, as shown in summary in APPENDIX II [189,192-194,196,197]. The insular cortices and caudate were reported to

exhibit increased activation in controls, during perception of neutral faces [196]; in my studies, I demonstrated increased activation in caudate in the low PLE group, but also increased activation in the right insular cortex in the high PLE group, during perception of angry faces. The right parahippocampal gyrus, was also observed to show increased activation in controls during perception of fearful faces [193]; in my studies, I noticed increased activation in the right parahippocampal gyrus in the low PLE group during perception of angry faces. These observations provide evidence for the presence of a potential ***extended psychosis phenotype*** encompassing prodromal and clinical presentations. The plethora of regions described in the schizophrenia literature of face tasks, which were not included in my findings, is also anticipated: a broader selection of brain areas seen in chronic psychosis can represent an epiphenomenon of the illness (e.g. linked to the presence of psychotic symptomatology) or even caused by events unrelated to the pathological process (e.g. antipsychotic treatment).

Following a different line of research, it is of note that BA10 (superior frontal cortex), BA13 (insular cortex) and BA19 (parahippocampal gyrus) - some of the BAs that encompassed the ROIs resulted in my study - are widely represented in ***various structural neuroimaging comparisons between childhood, adolescence and adulthood*** [216] [see APPENDIX III]. This finding is in agreement with the neurodevelopmental model of psychosis. If I consider that psychosis is associated with a multitude of developmental pitfalls, which can be conceptualised as abnormal maturation of the developing brain neurocircuitry, it is highly expected that brain areas showing larger structural changes during this process, would also show aberrant patterns of activation, consistent with the extended psychosis phenotype.

5.5.3. Studies of CANTAB Measures

Findings from my CANTAB studies can shed some more light to the interpretation of my fMRI results.

General Stratification: During the AGN, the low PLE group exhibited higher scores of omissions, compared to the high PLE group at BL, suggestive of a reduced inhibitory control, which is not accounted by my cross-sectional neuroimaging finding of reduced insular activation. On the contrary, a decrease in AGN scores from BL to FU seen in both the high PLE and low PLE groups, which corresponds to an improvement in affective/inhibitory control, could be partially accounted by a decrease in limbic activation from BL to FU in the high PLE group, and by an increase in prefrontal activation from BL to FU in the low PLE group. This observation is supported by the knowledge that affective tasks are largely mediated by limbic areas of the brain, while inhibitory control is largely mediated by the prefrontal cortices. Hyperactivation in the limbic system can account for an inability to regulate emotions, and as

discussed earlier, emotion regulation difficulties can be at the core of vulnerability to psychosis [51].

Specific Stratification: During the CGT, the low PLE group showed a better risk adjustment at BL which is not accounted by any of my cross-sectional neuroimaging findings at BL (reduced cerebellar activation and increased insular activation in the low PLE group). Similarly, an increase in CGT scores from BL to FU seen in both the high PLE and low PLE groups, is not accounted by a decrease in insular activation from BL to FU in the high PLE group.

5.5.4. Limitations

My study is not free of limitations. These are discussed below.

- *Characterisation of my high and low PLE groups.* In both stratification strategies, I selected high and low scorers of CAPE42 questionnaire as an attempt to identify the two most polarised groups which would best represent the 'prodromal psychotic' and 'healthy controls' phenotypes. However, it turned out that my high PLE group did not indeed score too high in the selected scores. The high PLE general stratification group had a mean score of 111.64 (ranging 91-182) compared with a theoretical maximum score of 294. Similarly, the high PLE specific stratification group had a mean score of 4.85 (ranging 3-16) compared with a theoretical maximum of 21. Obviously, given these scores, one can suggest a low degree of 'pre-psychotic' phenomenology in my high PLE groups, which introduces limitations to conducting comparisons with the low PLE groups, and discovering any differentiation at a brain activation level.

- *Evolution of PLE.* My stratification was based on CAPE scores at age 19; as no similar scores were available at age 14, therefore I could not track the evolution of PLE between the two timepoints.

- *Natural history of PLE.* In my studies, I have viewed the high-PLE phenotype as a proxy for the ARMS for psychosis; however, as discussed earlier, PLE can have multiple clinical outcomes, thus leading to a variety of psychopathologies, other than psychosis, or even resolve completely.

- *Transition to psychosis.* Lack of any longitudinal clinical data which could signal transition to psychosis introduces reasonable scepticism in the interpretation of my results, as to which extent my high PLE group is representative of an UHR for psychosis population. As discussed earlier, literature suggests that in the majority of cases, PLE resolve without any sequelae.

- *Sample characteristics.* Additional limitations might be sought in the higher representation of the male gender in my low PLE vs high PLE groups: 56.4% vs 33.6% (general stratification); 55.5% vs 41.5% (specific stratification). Male preponderance is however a common epidemiological trend in this clinical field [242]. Similarly, the IMAGEN design had applied very stringent exclusion criteria during the selection of participants, eliminating almost every possible medical and psychiatric co-morbidity (see **Table 2**). This has consequently resulted in a population of 'extremely healthy' adolescents, which might not be entirely representative of the general populations, thus introducing an element of bias.

- *Appropriateness of the Face Task.* Also, the relevance of the Face Task as a paradigm for the study of an important emotional aspect of quotidian social behaviour, might come with limitations, which can further reduce the clinical significance of my findings.

5.5.5. Summary of Discussion

Adolescents with high levels of PLE who underwent a faces task, demonstrate hyperactivation of insular cortical areas at BL, hypoactivation of prefrontal and limbic cortical areas and striatal subcortical areas at FU, and a decrease in limbic activation from BL to FU. The later might represent an *aberrant developmental process,* under-recruiting critical limbic areas during perception of emotional faces. These findings reinforce the role of prefrontal and limbic cortices in the aetiology of psychosis, beyond the bounds of the illness phenotype or the use of antipsychotic medication. The ongoing follow up of this sample will permit the further testing of this change as a useful brain biomarker for the psychosis or other psychiatric phenotypes.

Chapter VI: The Reward Task Study

6.1. Overview

Objective

To examine the neuroimaging profile of healthy adolescents with an increased presence of Psychotic-Like Experiences (PLE), during a reward cognitive task.

Method

1,434 adolescents were assessed at 2 timepoints using functional MRI during a Monetary Incentive Delay (MID) task at age 14 and 19 years. The sample was stratified into two groups of high PLE and low PLE based on their scores on the CAPE-42 questionnaire at age 19. A general and specific stratification was applied, the general stratification used the CAPE Total Score, while the specific stratification used a CAPE Score of 3 specific clinically significant items. The first level analysis focused on two pre-defined contrasts of [Anticipation of Large Win] – [Anticipation of No Win] and [Feedback of Large Win] – [Feedback of No Win]. The second level analysis examined between-group differences using an a priori defined region of interest approach (ROIs) within the reward network. I performed a factorial analysis to examine the main effects of *group*, *time* and their interaction on brain activation. Additionally, I performed an exploratory analysis, by employing both a cross-sectional design to compare brain activation levels between the high PLE and low PLE groups at ages 14 and 19, and a longitudinal design to compare brain activation levels between the two timepoints.

6.2. Results of fMRI Analysis

The following ROIs were initially identified through the literature of reward processing in psychosis and UHR for psychosis [102,103] and subsequently filtered through the second-level analysis. The ROIs listed here [MNI coordinates] showed differences in brain activation between groups (high PLE vs low PLE) and timepoints (BL vs FU). The main effect of *group, time* and the interaction of *group*time* on brain activation levels was examined by employing a mixed model 2-way ANOVA, and post-hoc paired/independent T-tests.

General Stratification ROIs

[33 41 40] Right Frontal Lobe, Middle Frontal Gyrus, BA09 (BL, Feedback)

[33 44 31] Right Frontal Lobe, Middle Frontal Gyrus, BA09 (BL, Feedback)

[-36 47 31] Left Frontal Lobe, Middle Frontal Gyrus, BA10 (BL, Feedback)

[-12 -28 40] Left Limbic Cortex, Cingulate Gyrus, BA31 (BL, Feedback)

[9 8 1] Right Caudate Head (FU, Anticipation)

Specific Stratification ROIs

[57 -46 -14] Right Temporal Lobe, Inferior Temporal Gyrus, BA20/37 (BL, Feedback)

[-30 -64 -32] Left Cerebellum, Uvula (BL, Feedback)

[-24 68 -8] Left Frontal Lobe, Superior Frontal Gyrus, BA10 (FU, Anticipation)

6.2.1. Retrospective Control for Multiple Testing

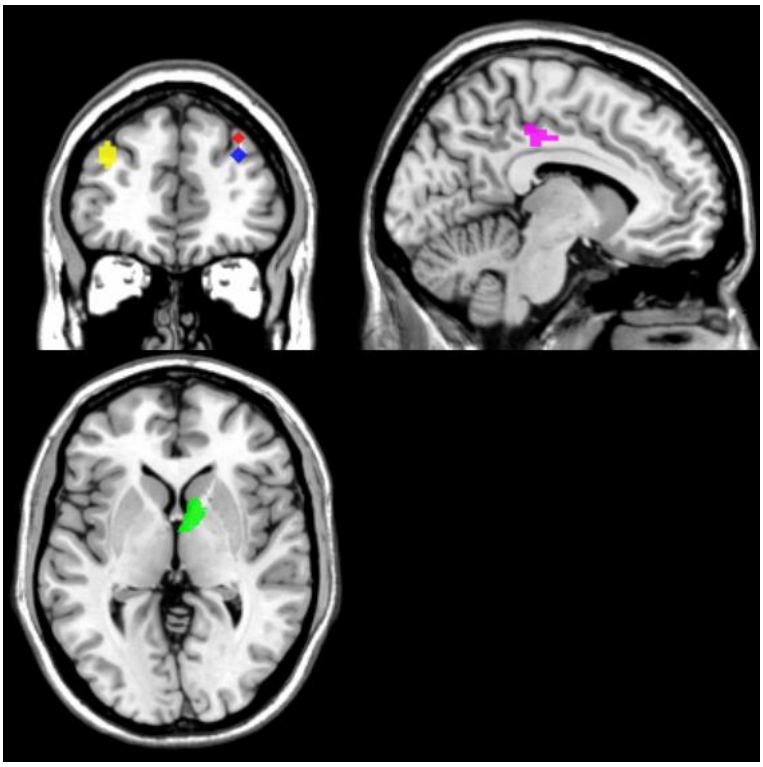
As multiple ROIs resulted from my Analysis, I performed a retrospective correction of the statistical significance threshold of the whole brain analysis, at a contrast level. As six ROIs were identified in the feedback contrast, and two in the anticipation contrast, I applied this correction to both contrasts. I used a Bonferroni correction, introducing a new level of statistical significance at 0.008 (0.05 / 6) for the feedback contrast and a level of statistical significance at 0.025 (0.05 / 2) for the anticipation contrast. As this approach is considered to be overly conservative, I report data from all eight ROIs, noting however that [33 41 40] and [33 44 31] did not survive the updated threshold of 0.008, corrected for multiple testing.

6.2.2. General Stratification

Figure 4: MID Study, ROIs selected for Analysis, General Stratification

BASELINE
[33 41 40] Right Middle Frontal Gyrus
(L>H, Feedback)
[33 44 31] Right Middle Frontal Gyrus
(L>H, Feedback)
[-36 47 31] Left Middle Frontal Gyrus
(L>H, Feedback)
[-12 -28 40] Left Cingulate Gyrus
(L>H, Feedback)

FOLLOW-UP
[9 8 1] Right Caudate Head
(L>H, Anticipation)



For more detailed illustrations see APPENDIX XXIII: General Stratification

Right Middle Frontal Gyrus [33 41 40]

There was an interaction effect of *group*time* [*F*(1, 93)=7.448, p=0.008], which was driven by a differential change in brain activation from *BL to FU,* showing significant *increase* in the high PLE group (t=-3.18, p=0.003) and non-significant decrease in the low PLE group. Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group at *BL during feedback* (t=-5.069, p<0.0001).

Right Middle Frontal Gyrus [33 44 31]

There was a main effect of *time* [*F*(1, 93)=5.009, p=0.028], which was driven by an *increase* in brain activation from BL to FU, significant only for the high PLE group (t=-2.902, p=0.006). Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group at *BL during feedback* (t=-3.029, p=0.003).

Left Middle Frontal Gyurs [-36 47 31]

There was a main effect of *time* [*F*(1, 93)=5.559, p=0.02], which was driven by an *increase* in brain activation from *BL to FU*, significant only for the high PLE group (t=-2.851, p=0.007). Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group at *BL during feedback* (t=-2.818, p=0.005).

Left Cingulate Gyrus [-12 -28 40]

No effects of *group*time*, *group* nor *time* were reported. Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group at *BL during feedback* (t=-2.82, p=0.005).

Right Caudate Head [9 8 1]

No effects of *group*time*, *group* nor *time* were reported. Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group at *FU during anticipation* (t=-2.846, p=0.005).

Table 10: MID Study, Factorial Analysis, Mixed Model 2-Way ANOVA, General Stratification

	Type III Sum of Squares	df	Mean Square	F	Sig.	r
Caudate ROI [9 8 1] Brain Activation, General Stratification, Anticipation						
GROUP	1.100	1	1.100	2.791	0.099*	0.181
TIME	1.684	1	1.684	1.635	0.205*	0.140
GROUP * TIME	1.593	1	1.593	1.546	0.217*	0.136
Error(GROUP)	32.311	82	0.394			
Error(TIME)	84.455	82	1.030			
Frontal ROI [33 41 40] Brain Activation, General Stratification, Feedback						
GROUP	4.108	1	4.108	3.598	0.061*	0.193
TIME	7.632	1	7.632	1.527	0.220*	0.127
GROUP * TIME	37.236	1	37.236	7.448	0.008	0.272
Error(GROUP)	106.187	93	1.142			
Error(TIME)	464.966	93	5.000			
Frontal ROI [33 44 31] Brain Activation, General Stratification, Feedback						
GROUP	2.323	1	2.323	1.821	0.180*	0.139
TIME	25.604	1	25.604	5.009	0.028	0.226
GROUP * TIME	8.606	1	8.606	1.684	0.198*	0.133
Error(GROUP)	118.659	93	1.276			
Error(TIME)	475.398	93	5.112			
Frontal ROI [-36 47 31] Brain Activation, General Stratification, Feedback						
GROUP	2.24	1	2.24	1.77	0.187*	0.137
TIME	33.354	1	33.354	5.559	0.020	0.237
GROUP * TIME	19.871	1	19.871	3.312	0.072*	0.185
Error(GROUP)	117.68	93	1.265			
Error(TIME)	558.029	93	6			
Limbic ROI [-12 -28 40] Brain Activation, General Stratification, Feedback						
GROUP	0.839	1	0.839	0.801	0.373*	0.092
TIME	5.911	1	5.911	1.906	0.171*	0.142
GROUP * TIME	0.086	1	0.086	0.028	0.868*	0.017
Error(GROUP)	97.359	93	1.047			
Error(TIME)	288.332	93	3.100			

Abbreviations
df: degrees of Freedom; **F:** F-ratio; **(*)**: not statistically significant at a p=0.05 level; **r:** Pearson's correlation coefficient;

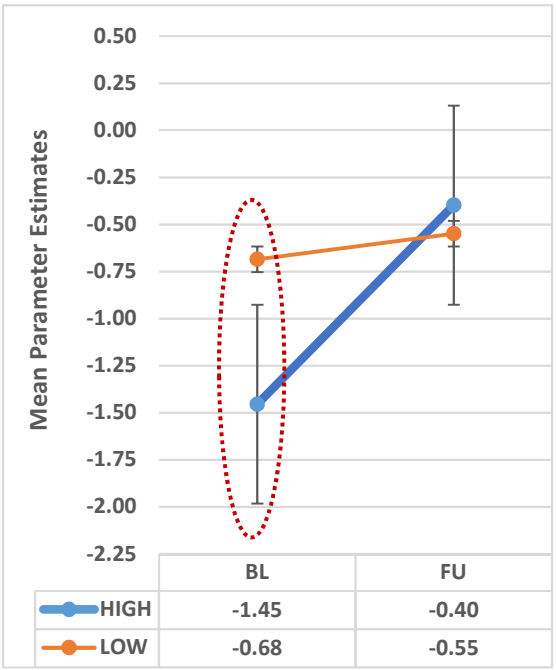
For a table of fROIs brain analysis results see APPENDIX XVII: General Stratification

For a table of cross-sectional analysis results see APPENDIX XVIII: General Stratification

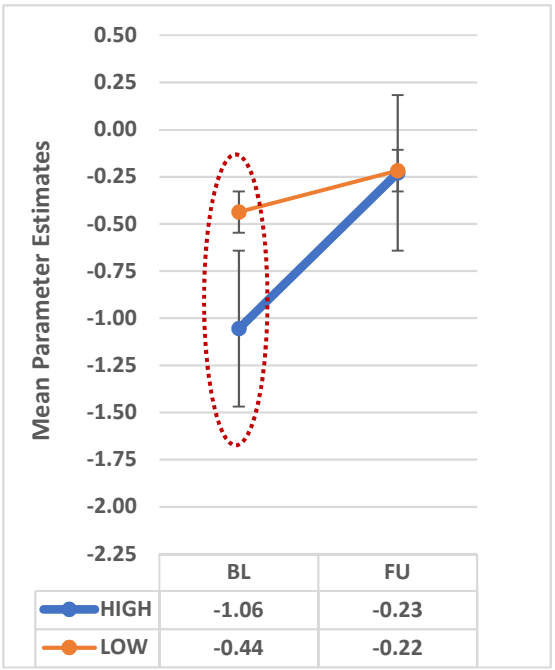
For a table of longitudinal analysis results see APPENDIX XIX: General Stratification

Graph 6: MID Study, Longitudinal Analysis Graphs, General Stratification

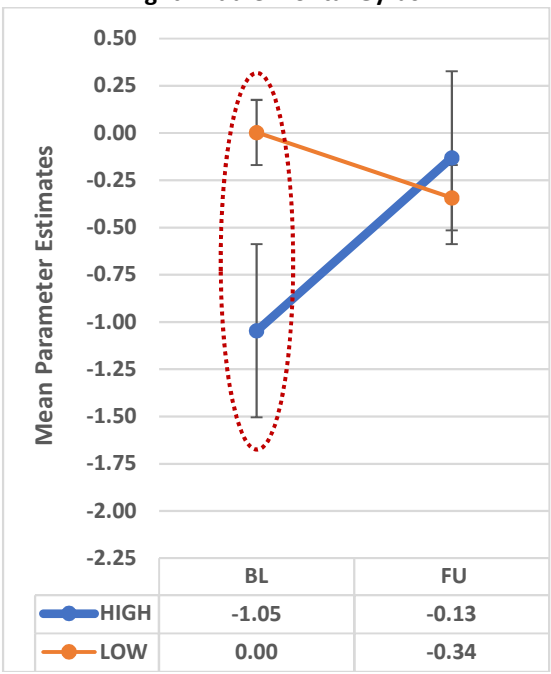
Brain Activation at BL and FU, ROI [-36 47 31], Left Middle Frontal Gyrus



Brain Activation at BL and FU, ROI [33 44 31], Right Middle Frontal Gyrus



Brain Activation at BL and FU, ROI [33 41 40], Right Middle Frontal Gyrus



Longitudinal changes are statistically significant (p<.05) for the **High PLE Group** only (thick line); **encircled** (red dotted line) are statistically significant cross-sectional differences (p<.05); SE bars are displayed.

Table 11: MID Study, Summary of Findings, General Stratification

Brain ROI	Factorial Analysis (sign. effects)	Exploratory Analysis		
		BL state	BL to FU changes	FU state
Right Middle Frontal Gyrus **[33 41 40]**	**Group*Time**	**L>H** Feedback	**H ↑** **L ↓** NS	
Right Middle Frontal Gyrus **[33 44 31]**	**Time**	**L>H** Feedback	**H ↑** **L ↑** NS	
Left Middle Frontal Gyrus **[-36 47 31]**	**Time**	**L>H** Feedback	**H ↑** **L ↑** NS	
Left Limbic Cortex **[-12 -28 40]**		**L>H** Feedback		
Right Caudate Head **[9 8 1]**				**L>H** Anticipation

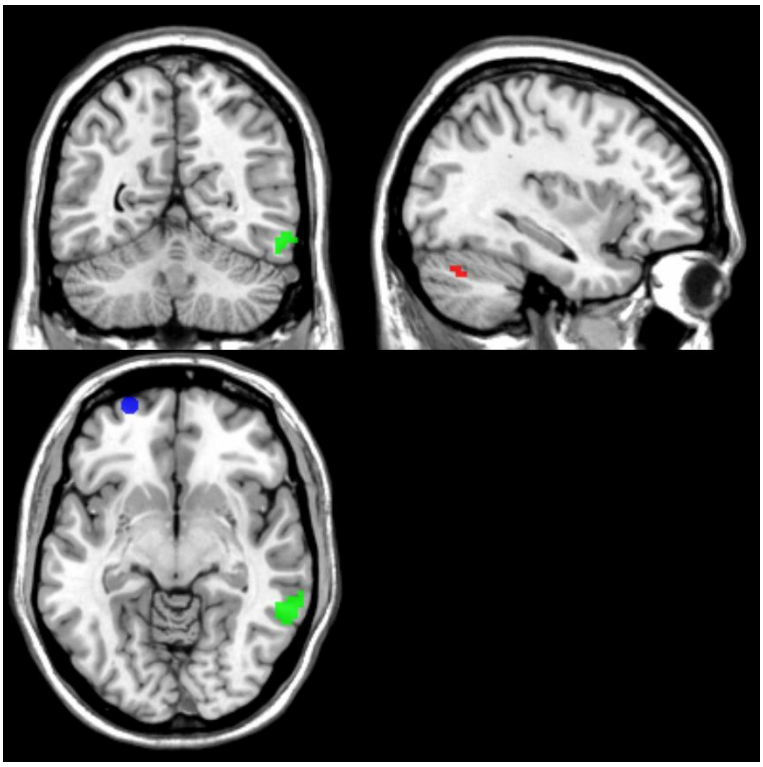
H: High PLE Group; **L**: Low PLE Group;
↑: Increase in brain activation (statistically significant);
↑ NS: Increase in brain activation (statistically non-significant);
↓: Decrease in brain activation (statistically significant);
↓ NS: Decrease in brain activation (statistically non-significant)

6.2.3. Specific Stratification

Figure 5: MID Study, ROIs selected for Analysis, Specific Stratification

BASELINE
[57 -46 -14] Right Inferior Temporal Gyrus
(L>H, Feedback)
[-30 -64 -32] Left Cerebellar Uvula
(L>H, Feedback)

FOLLOW-UP
[-24 68 -8] Left Superior Frontal Gyrus
(L>H, Anticipation)



For more detailed illustrations see APPENDIX XXIV: Specific Stratification

Right Inferior Temporal Gyrus [57 -46 -14]

No effects of *group*time*, *group* nor *time* were reported. Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group at *BL during feedback* (t=-3.126, p=0.002).

Left Cerebellar Uvula [-30 -64 -32]

There was an interaction effect of group*time [F(1, 218)=4.889, p=0.028], which was driven by differential change in brain activation from BL to FU, showing significant decrease in the low PLE group (t=2.249, p=0.027)., and non-significant increase in the high PLE group. Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group at *BL during feedback* (t=-3.048, p=0.002).

Left Superior Frontal Gyrus [-24 68 -8]

No effects of *group*time*, *group* nor *time* were reported. Additional exploratory analysis exhibited higher brain activation of the low PLE group compared to the high PLE group at *FU during anticipation* (t=-2.211, p=0.028).

Table 12: MID Study, Factorial Analysis, Mixed Model 2-Way ANOVA, Specific Stratification

	Type III Sum of Squares	df	Mean Square	F	Sig.	r
Frontal ROI [-24 68 -8] Brain Activation, Specific Stratification, Anticipation						
GROUP	0.326	1	0.326	0.747	0.388*	0.059
TIME	6.548	1	6.548	3.271	0.072*	0.122
GROUP * TIME	3.365	1	3.365	1.681	0.196*	0.088
Error(GROUP)	93.830	215	0.436			
Error(TIME)	430.378	215	2.002			
Temporal ROI [57 -46 -14] Brain Activation, Specific Stratification, Feedback						
GROUP	3.155	1	3.155	3.091	0.080*	0.118
TIME	9.444	1	9.444	2.760	0.098*	0.112
GROUP * TIME	2.148	1	2.148	0.628	0.429*	0.054
Error(GROUP)	222.561	218	1.021			
Error(TIME)	745.917	218	3.422			
Cerebellar ROI [-30 -64 -32] Brain Activation, Specific Stratification, Feedback						
GROUP	1.217	1	1.217	0.921	0.338*	0.065
TIME	5.689	1	5.689	1.184	0.278*	0.074
GROUP * TIME	23.486	1	23.486	4.889	0.028	0.148
Error(GROUP)	288.073	218	1.321			
Error(TIME)	1047.221	218	4.804			

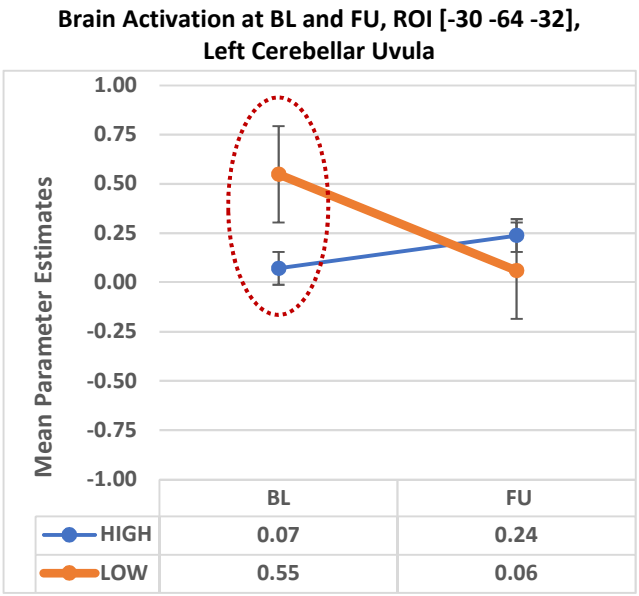
Abbreviations
df: degrees of Freedom; **F:** F-ratio; **(*)**: not statistically significant at a p=0.05 level; **r:** Pearson's correlation coefficient;

For a table of fROIs brain analysis results see APPENDIX XVII: Specific Stratification

For a table of cross-sectional analysis results see APPENDIX XVIII: Specific Stratification

For a table of longitudinal analysis results see APPENDIX XIX: Specific Stratification

Graph 7: MID Study, Longitudinal Analysis Graph, Specific Stratification



Longitudinal changes are statistically significant (p<.05) for the **Low PLE Group** only (thick line); **encircled** (red dotted line) are statistically significant cross-sectional differences (p<.05); SE bars are displayed.

Table 13: MID Study, Summary of Findings, Specific Stratification

Brain ROI	Factorial Analysis (sign. effects)	Exploratory Analysis		
		BL state	BL to FU changes	FU state
Right Inferior Temporal Gyrus **[57 -46 -14]**		**L>H** Feedback		
Left Cerebellum **[-30 -64 -32]**	**Group*Time**	**L>H** Feedback	**H** ↑ NS **L** ↓	
Left Superior Frontal Gyrus **[-24 68 -8]**				**L>H** Anticipation

H: High PLE Group; **L**: Low PLE Group;
↑: Increase in brain activation (statistically significant);
↑ NS: Increase in brain activation (statistically non-significant);
↓: Decrease in brain activation (statistically significant);
↓ NS: Decrease in brain activation (statistically non-significant)

6.3. Results of CANTAB Measures

Results of CANTAB measures are already presented in 5.3 Results of CANTAB Measures.

6.4. Correlations

In exploratory analysis, I investigated whether brain activation levels for my identified fROIs correlated with selected CAPE and CANTAB scores. The strength of these correlations proved weak, though numerous statistically significant results were generated. Most notably, baseline BOLD signals of the Right Middle Frontal Gyrus ROI [33 41 40] negatively correlated with CAPE grand total scores (rho=-0.373, p<0.0001) and CAPE 3-items scores (rho=-0.296, p=0.004); also, follow-up BOLD signals of the Right Caudate Head ROI [9 8 1] negatively correlated with CAPE grand total scores (rho=-0.235, p=0.005) and CAPE 3-items scores (rho=0.218, p=0.009).

See APPENDIX XXV

6.5. Discussion

6.5.1. Overview of fMRI Studies

The primary finding, if one looks at ROIs based on the general PLE stratification, is that brain areas showed differences at BL and FU. *In summary,* in the high PLE group, an early state of hypoactivation in left [-36 47 31] and right prefrontal [33 44 31] [33 41 40] and left limbic [-12 -28 40] cortical areas, was replaced by a later state of hypoactivation in right caudate [9 8 1], when the general stratification was applied.

Secondary findings, if one looks at ROIs based on the specific stratification, are that again *different* brain areas showed differences at BL and FU. *In summary,* in the high PLE group, an early state of hypoactivation in right temporal cortical [57 -46 -14] and left cerebellar [-30 -64 -32] areas, was replaced by a later state of hypoactivation in a left prefrontal area [-24 68 -8], when the specific stratification was applied.

My longitudinal studies revealed differences in brain level activities between BL and FU in relatively fewer brain areas, compared to the ones identified in the cross-sectional studies. *In summary,* in the high PLE group, there was an increase in brain activation between BL and FU in left and right prefrontal areas.

My results nevertheless provide a confirmation of my research hypothesis as engagement of prefrontal, temporal, cingulate and striatal areas was reaffirmed.

6.5.2. Interpretation of fMRI Results

Adolescents with high levels of PLEs at age 19 years demonstrated a significant increase in prefrontal activation during a reward processing task between the ages of 14 and 19, compared to non-significant changes seen in adolescents with low levels of PLE. The high PLE group also exhibited a decreased activation of the head of caudate relative to the low PLE group at age 19 years. The decrease in the striatal activation is in agreement with my hypothesis and has been observed in the literature [42]. However, the increase in frontal activation (between the ages of 14 and 19) is novel. Previous studies in early adolescent high risk populations have suggested a decreased frontal brain activation, compared to controls [102]; this is in line with my findings of lower frontal activation (left and right middle frontal gyri) in my high PLE group, compared to the low PLE group at age 14.

However, it needs to be borne in mind that I am assessing a non-clinical group and one can speculate that I may be observing a compensatory mechanism in operation. Certainly, there is a contemporary view that suggests that abnormal perceptions may be a relatively common occurrence, and in most cases, they are appropriately contextualised, and an abnormal belief

or experience does not arise. In this case of adolescents with high levels of PLE, these are still largely being appropriately contextualised, as they have not developed to a clinical intensity. Indeed, the pattern of decreased striatal activation and increased prefrontal activation supports the suggestion that the evolution of clinically relevant psychotic symptoms requires not only a deficit in striatal reward processing but, also a failure of prefrontal executive processes [243,244]. Thus, this prefrontal activation serves as a proxy of an efficient executive function and as a compensatory mechanism to ensure that any unusual experiences secondary to reward processing deficits do not become fixed and understood outside of the current context. It's probable that the failure of the latter process leads to clinically relevant symptoms. The lack of any performance differences in executive functioning between the low and high PLE adolescent groups (at the age of 19) also lends additional support to this view. However, other possibilities are that this pattern of change in processing reward engages PFC and striatum in a different way to generate PLEs in these subjects; or even that these differences reflect the allocation of potential resources in a proactive healthy way.

Considering my high PLE group results from a neuro-developmental point of view, one needs to distinguish between ***states*** (patterns of brain activation which are observed only in a particular timepoint) versus ***traits*** (patterns of brain activation which persist along various timepoints).

In my cross-sectional studies, I revealed different hypoactivation ***states*** at different timepoints, with an observed narrowing of the brain areas involved at FU compared to BL. This might represent a developmental process in the course of the prodromal psychosis phenotype, during which the majority of the areas showing aberrant activation at an BL (frontal and limbic), might become subject to a ***'compensatory' developmental process*** resulting from brain maturation. However, under an opposing ***'aberrant' developmental process***, other areas of hypoactivation (caudate) can emerge at a later phase of brain development and thus might represent a clinically significant marker of future emergence of psychosis. Striatal hypoactivation is linked to compromised motivational behaviour, and is indeed a finding shared by UHR for psychosis and schizophrenia populations [103]. This is consistent with the observation that striatum as one of the key components of the cortico-striatal-thalamic circuitry plays a major role in reward-driven behaviour [245].

Hypoactivation of the frontal lobes (hypofrontality) and ***dysconnectivity of fronto-striatal circuitry*** were previously discussed in 5.5.2. Interpretation of fMRI Results. My longitudinal studies indeed confirmed that three frontal areas, showing hypoactivation in the high PLE group at BL, also manifested significant increase in activation from BL to FU. This change might represent the outcome of a ***'compensatory' developmental process***, *either targeting brain*

areas showing an activation deficit at an early phase or allowing cognitive control mechanisms to contextualise the PLE, in order to prevent an evolution to clinical symptoms. As discussed earlier, a reward-associated dysregulation can be compensated by recruitment of additional prefrontal areas, in UHR for psychosis subjects [106].

Ethological observations have traditionally distinguished between ***appetitive*** (*anticipation or reward, motivational phase*) and ***consummatory*** (*outcome/feedback of reward, hedonic response*) stages of ***reward processing***; Basic research in healthy individuals has revealed that reward anticipation and outcomes may differentially recruit distinct regions that lie along the trajectory of ascending dopamine neurons; anticipation of reward vs non-reward activated foci in the ventral striatum (including the nucleus accumbens), while reward vs non-reward outcomes activated foci in the VMPFC [246,247]. Additional research has revealed that monetary reward outcomes strongly activated the thalamus, while social reward outcomes were associated with pronounced bilateral amygdalae activation [248]. Indeed, in my studies, three ROIs which resulted from the feedback contrast were located in middle fontal gyri; one ROI which resulted from the anticipation contrast was located in the dorsal striatum (caudate). A recent fMRI study from the IMAGEN sample [108] showed that during the MID task (anticipation large win - no win), at age 14, the high psychosis proneness group, showed increased activation in the right anterior/middle cingulate gyrus and decreased activation in the left fusiform gyrus. It is of note however, that the authors of this study employed a smaller sample, assessed PLE at age 14 and used a less extended assessment tool for PLE focusing on perceptual abnormalities and delusional thoughts. Additionally, another study from the IMAGEN sample [249] identified a network containing a core striatal node and cortical nodes facilitating outcome prediction and response preparation at age 14; striatal areas were preferentially associated with hyperactivity symptoms; this highlights the importance of reward circuit elements in a variety of psychopathologies.

The ***dopamine hypothesis of schizophrenia***, specified subcortical hyper-dopaminergia combined with prefrontal hypo-dopaminergia as the cardinal features of neuro-pathology of schizophrenia; this has been modified by inclusion of a presynaptic striatal dopamine dysregulation conceptualised as the final common pathway responsible for the mis-appraisal of stimuli thus resulting in the emergence psychosis [199]. The ***anhedonia hypothesis***, postulates that dopamine plays a critical role in the subjective pleasure associated with positive rewards, and has been fundamental in the neurobiology of addiction and the understanding of incentive motivation [250]. The two hypotheses converge in schizophrenia, where observed motivational impairments and reward-processing abnormalities [198] were linked to multiple aberrant cortical-striatal interactions [251]. In my study, I showed that aberrant activation in this neural

circuit (frontal areas and caudate head) is present at ages 14 and 19 in subjects with a prodromal psychotic phenotype. This observation supports the presence of brain biomarkers across the whole spectrum of the extended psychosis phenotype.

The ***schizophrenia literature*** of neuroimaging studies involving reward tasks, has revealed a multitude of ROIs in various BAs, with differences in brain activation between patients with schizophrenia or first-episode psychosis and healthy controls, as shown in summary in APPENDIX II [202,205-212]. All ROIs described in the present study (probably at the exception of the cerebellar ones), fall within BAs identified in schizophrenia neuroimaging studies of reward tasks, as hosting ROIs with differential brain activation between psychotic and non-psychotic subjects. These include BA09 (dorsolateral prefrontal cortex), BA10 (anterior prefrontal cortex), BA20 (inferior temporal gyrus), BA31 (dorsal posterior cingulate area) and Caudate Head. These observations provide evidence for the presence of an ***extended psychosis phenotype*** encompassing prodromal and clinical presentations. The plethora of BAs described in the schizophrenia literature of reward tasks, which were not included in my findings is also anticipated: a broader selection of brain areas seen in chronic psychosis can represent an epiphenomenon of the illness (e.g. linked to the presence of psychotic symptomatology) or even caused by events unrelated to the pathological process (e.g. antipsychotic treatment).

The role of the ***cerebellum*** in schizophrenia was previously discussed in 5.5.2. Interpretation of fMRI Results. Consequently, my finding of BL hypoactivation in a left cerebellar ROI in the high PLE group might be an early indication of a pathology that could later generate a more pronounced deficit.

Following a different line of research, it is of note that BA09 (dorsolateral prefrontal cortex), BA10 (anterior prefrontal cortex) and BA20 (inferior temporal gyrus) - some of the BAs that encompassed the ROIs resulted in my study - are widely represented in ***various structural neuroimaging comparisons between childhood, adolescence and adulthood*** [216], while BA31 (posterior cingulate cortex) hosts one of the largest clusters showing changes between childhood and adolescence [218] [see APPENDIX III]. This finding is in agreement with the neurodevelopmental model of psychosis. If I consider that psychosis is associated with a multitude of developmental pitfalls, which can be conceptualised as abnormal maturation of the developing brain neurocircuitry, it is highly expected that brain areas showing larger structural changes during this process, would also show aberrant patterns of activation, consistent with the extended psychosis phenotype.

6.5.3. Studies of CANTAB Measures

Findings from my CANTAB studies can shed some more light to the interpretation of my fMRI results.

General Stratification: During the AGN, the low PLE group showed higher scores of omissions compared to the high PLE group at BL, suggestive of a reduced inhibitory control, despite the cross-sectional neuroimaging finding of increased brain activation of frontal ROIs in the low PLE group compared to the high PLE group at BL. On the contrary, a decrease in AGN scores from BL to FU seen in both the high and low PLE groups, which corresponds to an improvement in affective/inhibitory control, can be partially accounted by the longitudinal neuroimaging finding of an increase in brain activation of prefrontal ROIs from BL to FU, significant only for the high PLE group. This lends support to the proposal that there were no significant differences in *explicit* cognitive control between the high and low PLE groups, compared to an *implicit* compensatory cognitive control mechanism, seen only in the high PLE group.

Specific Stratification: During the CGT, the low PLE group showed a better risk adjustment at BL, which is not accounted by any of the cross-sectional neuroimaging findings at BL (increased temporal and cerebellar activation in the low PLE group). The longitudinal CGT changes do not find any match, as only a cerebellar ROI resulting from the specific classification showed longitudinal changes (significant only for the low PLE group).

6.5.4. Limitations

My study is not free of limitations. These were discussed in detail in 5.5.4. Limitations. In addition, the relevance of the MID task as a paradigm for the study of quotidian reward-related behaviour, might come with limitations, which can further reduce the clinical significance of my findings.

6.5.5. Summary of Discussion

Adolescents with high levels of PLE performing a reward processing task, demonstrate hypoactivation of prefrontal and limbic areas at BL, hypoactivation of the caudate at FU, and an increase in prefrontal activation from BL to FU. The later might represent a '*compensatory' developmental process*, permitting cognitive control mechanisms to contextualise the PLE, sufficient to preclude an evolution to clinical intensity; an observation which is consistent with the *aberrant salience model of psychosis*. These findings reinforce the role of components of the brain reward circuit, such as the prefrontal cortex and the striatum in the aetiology of psychosis, beyond the bounds of the illness phenotype or the use of antipsychotic medication. The ongoing follow up of this sample will permit the further testing of this change as a useful brain biomarker for the psychosis or other psychiatric phenotypes.

Chapter VII: Conclusions

FT Studies

Adolescents presenting with elevated overall PLE scores at age 19 years exhibited an early state (BL) of hyperactivation in right insular cortical areas, during perception of angry faces; this was replaced by a later state (FU) of hypoactivation in right prefrontal and right limbic cortical areas and left striatal subcortical areas, during perception of angry faces. There was a decrease in activation of right limbic cortical areas, from BL to FU, in the high general PLE group.

Adolescents presenting with elevated specific PLE scores at age 19 years exhibited an early state (BL) of hyperactivation in left cerebellar and hypoactivation in left insular cortical areas, during perception of angry faces; this was replaced by a later state (FU) of hypoactivation in left cerebellar and left insular cortical areas, during perception of angry faces. There was a decrease in activation of left insular cortical areas, from BL to FU, in the high specific PLE group.

These results suggest evidence of *aberrant changes* during adolescent development with reduced limbic and insular activation over time; this might reflect an under-recruitment of critical areas during perception of emotional faces. My findings reinforce the role of prefrontal and limbic cortices in the aetiology of psychosis, beyond the bounds of the illness phenotype and without the confounds of the impact of the illness or the use of antipsychotic medication.

Table 14: FT Studies, Summary of Findings, High PLE Group

Brain ROI	Stratification	BL state	BL to FU changes	FU state	Comment
Right Insular Cortex **[42 8 -14]**	General	Hyper-active	↓ NS		
Left Caudate Body **[-12 5 10]**	General			Hypo-active	
Right Superior Frontal Gyrus **[6 65 31]**	General		↑ NS	Hypo-active	Stable Deficit
Right Limbic Cortex **[33 -46 -5]**	General		↓	Hypo-active	Aberrant Developmental Process
Left Cerebellum **[-6 -73 -26]**	Specific	Hyper-active			
Left Insular Cortex **[-33 11 10]**	Specific	Hypo-active	↑ NS		
Left Cerebellum **[-15 -40 -44]**	Specific			Hypo-active	
Left Insular Cortex **[-33 17 -11]**	Specific		↓	Hypo-active	Aberrant Developmental Process

Hyper-active: High PLE Group shows greater brain activation than Low PLE Group
Hypo-active: Low PLE Group shows greater brain activation than High PLE Group
↑: Increase in brain activation (statistically significant);
↑ NS: Increase in brain activation (statistically non-significant);
↓: Decrease in brain activation (statistically significant);
↓ NS: Decrease in brain activation (statistically non-significant)

MID Studies

Adolescents presenting with elevated overall PLE scores at age 19 years exhibited an early state (BL) of hypoactivation in left and right prefrontal and left limbic cortical areas, during reward feedback; this was replaced by a later state (FU) of hypoactivation in right striatal subcortical areas, during the reward anticipation. There was also an increase in activation of left and right prefrontal areas, from BL to FU, in the high general PLE group.

Adolescents presenting with elevated specific PLE scores at age 19 years exhibited an early state (BL) of hypoactivation in right temporal cortical areas and left cerebellar areas, during reward feedback; this was replaced by a later state (FU) of hypoactivation in left prefrontal cortical areas, during reward anticipation.

These results suggest evidence of *compensatory changes* during adolescent development with increased prefrontal activation over time; this might allow cognitive control mechanisms to contextualise the PLE, so to prevent transition to clinically significant symptoms; an observation which is consistent with the *aberrant salience model of psychosis*. My findings reinforce the role of components of the brain reward circuit, such as the prefrontal cortex and the striatum in the aetiology of psychosis, beyond the bounds of the illness phenotype and without the confounds of the impact of the illness or the use of antipsychotic medication.

Table 15: MID Studies, Summary of Findings, High PLE Group

Brain ROI	Stratification Contrast	BL state	BL to FU changes	FU state	Comment
Right Middle Frontal Gyrus **[33 41 40]**	General, Feedback	Hypo-active	↑		Compensatory Developmental Process
Right Middle Frontal Gyrus **[33 44 31]**	General, Feedback	Hypo-active	↑		Compensatory Developmental Process
Left Middle Frontal Gyrus **[-36 47 31]**	General, Feedback	Hypo-active	↑		Compensatory Developmental Process
Left Limbic Cortex **[-12 -28 40]**	General, Feedback	Hypo-active			
Right Caudate Head **[9 8 1]**	General, Anticipation			Hypo-active	Aberrant Developmental Process
Right Inferior Temporal Gyrus **[57 -46 -14]**	Specific, Feedback	Hypo-active			
Left Cerebellum **[-30 -64 -32]**	Specific, Feedback	Hypo-active	↑ NS		
Left Superior Frontal Gyrus **[-24 68 -8]**	Specific, Anticipation			Hypo-active	

Hyper-active: High PLE Group shows greater brain activation than Low PLE Group
Hypo-active: Low PLE Group shows greater brain activation than High PLE Group
↑: Increase in brain activation (statistically significant);
↑ NS: Increase in brain activation (statistically non-significant);
↓: Decrease in brain activation (statistically significant);
↓ NS: Decrease in brain activation (statistically non-significant)

CANTAB Studies

Adolescents presenting with an elevated frequency of PLE at age 19 years exhibited an early state (BL) of enhanced inhibitory control and compromised risk-taking behaviour, compared to the low PLE group. There was an improvement in both cognitive domains from BL to FU, noted in both the high and low PLE groups. These results suggest evidence of a *compensatory change* during adolescent development, which could be accounted by the observed increased prefrontal activation and decreased limbic activation.

Table 16: CANTAB Studies, Summary of Findings, High PLE Group

CANTAB score	Stratification	BL state	BL to FU changes	FU state	Comment
AGN Total Omissions, Positive Stimuli	General	Lower Scores (enhanced inhibitory control)	↓		Improvement of inhibitory control
AGN Total Omissions, Negative Stimuli	General	Lower Scores (enhanced inhibitory control)	↓		Improvement of inhibitory control
CGT Risk Adjustment	Specific	Lower Scores (compromised risk-taking behaviour)	↑		Improvement of judgment in risk-taking behaviour

↑: Increase in CANTAB score (statistically significant);
↓: Decrease in CANTAB score (statistically significant)

My Project in Summary

I adopted the contemporary and widely accepted continuum model of psychosis, focussed on a healthy population with pre-clinical manifestations of the extended psychosis phenotype. The underlying idea was that biomarkers of psychosis, can be sought across the whole spectrum of this disorder, and not exclusively in those with clinically significant psychotic symptoms. An obvious repercussion of this approach is that the boundaries between *abnormal psychology* and *psychopathology* become quite blurred. This is, however, consistent with the continuum model, and offers the advantage of assessing larger numbers of individuals along the neurodevelopmental trajectory of adolescence, free of confounds from (a) illness chronicity (b) social / occupational / educational influences, and (c) the effects of exposure to antipsychotic medication. Taking this view into account, my findings add to the knowledge characterizing the associations of the neurodevelopmental trajectory with psychosis.

Psychotic-Like experiences (PLE) were chosen as a representative of the sub-clinical manifestations of the extended psychosis phenotype, in line with the continuum model of psychosis. There were no other proxy measures of PLE collected in this sample, and CAPE was added specifically for this purpose. As persistence of PLE has been predictive of increased rates of future transition to psychosis, this phenotype holds particular clinical significance. CAPE-42 was used as an appropriate tool to measure PLE, having exhibited adequate validity and reliability, added to its usability as a self-administered questionnaire. I do not claim that presence of PLE, reflected in high CAPE scores can predict transition to psychosis; however, early adolescent PLE are a recognised risk factor for psychosis.

As current research in psychosis has emphasized the importance of dysconnectivity between brain areas, I chose functional neuroimaging as my vehicle to investigate brain activity. I attempted to investigate the neural correlates of the prodromal psychosis phenotype by employing two well established cognitive tasks of *face and reward processing* along with functional neuroimaging.

The two tasks are different in terms of focus: the *face task* targets brain activation during processing of angry faces; the *reward task* singles out brain activation during anticipation and feedback of possible monetary gain. However, as demonstrated in the psychosis literature, both tasks have the potential to unmask disrupted interactions between higher / prefrontal cortical area and lower / subcortical areas (the striatum during reward tasks; the amygdala and related limbic areas during face / emotional tasks).

My results provide support of an *aberrant salience model of psychosis*. In order to contextualise emerging PLE and prevent transition to clinically significant symptoms, a

cognitive control mechanism recruits frontal cortical areas. In my reward study, this could be manifested as a compensatory increase in prefrontal activation between BL and FU during feedback, combined with a striatal hypoactivation at FU during anticipation. However, it is equally possible that cognitive control mechanisms fail to address an underlying aberrant salience process. In my face study, the latter might be demonstrated by a FU prefrontal hypoactivation state combined with an aberrant decrease in limbic activation between BL and FU, during perception of angry faces.

The limitations of my studies have been already discussed previously; to a great extent these drawbacks were inherited because I drew my data from a larger project (IMAGEN) initially designed to study various aspects of adolescent brain development and behaviour such as sensitivity to rewards, impulsivity and emotional processing. A larger cohort of adolescents would enable us to eventually assembly larger high and low PLE groups and increase the power of my analyses; an earlier age at BL timepoint (e.g. at years 11 of age), combined with the use of CAPE questionnaire at both BL and FU would permit a longer and more accurate observation of the evolution of PLE; finally, and most importantly, the longitudinal follow up of the high PLE group and the inclusion of transition to psychosis data would validate a neural characterisation of the UHR for psychosis population. I hope however that given all current shortcomings, my studies contributed to the neuroimaging literature of the extended psychosis phenotype, focusing at the prodromal boundary of this continuum.

Future Directions

I advocate further research in line with the above contemporary models of psychosis to confirm the presence and extend the list of similar brain biomarkers across the whole spectrum of the psychosis phenotype. Focus on prodromal psychotic manifestations provides however the advantage of studying psychosis beyond the bounds of the illness phenotype or the use of antipsychotic medication. Besides, early detection of high-risk individuals allows for the timely implementation of early interventions, which could steer a developmental trajectory away from the future psychotic outcome.

Current assessment of the ARMS is based almost exclusively on clinical interviews; the nature of these methods might account for the large variability in calculating transition rates to psychosis. The simple paradigm of the high PLE endophenotype offers however the opportunity to conceptualise a brain 'signature', by combining CAPE scores with selected CANTAB scores and functional neuroimaging markers; this could form the basis for modelling the risk of deviation towards psychosis and apply this model at an individual level.

There is an increasing interest in speaking of symptoms as dimensions rather than discrete psychopathological constructs or categorical diagnosis; the NIMH Research Domain Criteria (RDoC) conceptualises mental illness as disorders demarcated by symptoms, mapping onto cognitive systems and then to neural circuits. Evidence for these mechanism in these multiple levels of explanation can be quantified with the tools of cognitive science [252]. This approach leads towards a 'stratified' or 'personalised' psychiatry and relies on multi-dimensional representation of both definition of disorder and the clinical trajectories and outcomes [253].

By combining a brief self-administered questionnaire (such as CAPE), with other behavioural markers (such as selected CANTAB measures), functional neuroimaging, and potentially a genetic test, one could assembly a future screening toolkit with enhanced predictive value, for the reliable and swift detection of individuals at high risk for psychosis. I hope my research has contributed towards this direction.

Curriculum Vitae

Summary

I graduated in medicine in Thessaloniki, Greece and trained in general adult psychiatry in London under a residency scheme organized by Imperial College. I was next employed as research psychiatrist at the department of psychosis studies of the Institute of Psychiatry, Psychology and Neuroscience, King's College London, and later as a specialist registrar in psychiatry in a number of London teaching hospitals. More recently I moved to the pharmaceutical industry and held clinical development posts in the UK and Belgium. I am currently a Senior Global Medical Advisor for Lundbeck, based in Copenhagen, Denmark.

I have an overall clinical experience of 11 years (7 years in psychiatry, 1 year in neurology, 3 years in general medicine) and a clinical research experience of 5 years (in both academic and commercial settings).

Education & Training

2012-2018	Doctoral Studies, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, University of London
2007-2008	Cognitive Neuropsychology Masters, School of Psychology, Birkbeck College, University of London
2004-2008	Charing Cross Core Psychiatry Training Scheme, Imperial College London
1992-1998	Medical School, Aristotle University of Thessaloniki, Greece

Qualifications

Apr 2009	General Medical Council, Specialist Register under General Psychiatry
Mar 2009	Specialty Qualification in General Adult Psychiatry, Greece
Nov 2008	Masters in Cognitive Neuropsychology, London, UK
Jul 1998	Medical Doctor, Thessaloniki, Greece

Links

Professional Profile: https://uk.linkedin.com/in/evangelos-papanastasiou-0a522722

List of Publications: https://scholar.google.com/citations?user=JnIgJ1YAAAAJ&hl=en

Abbreviations

ACPC	Anterior Commissure-Posterior Commissure Plane
ADHD	Attention-Deficit Hyperactivity Disorder
ADRS	Adolescent Depression Rating Scale
ADT	Age Discrimination Task
AGFI	Adjusted Goodness of Fit Indices
AGN	Affective Go/NoGo Task
ALSPAC	Avon Longitudinal Study of Parents and Children
AMG	Amygdala(e)
ANOVA	Analysis of Variance
APS	Attenuated Psychotic Symptoms
APSS	Adolescent Psychotic-Like Symptom Screener
ARMS	At-Risk Mental State (for psychosis)
ASD	Autistic Spectrum Disorders
ASPIS	Athens Study of Psychosis Proneness and Incidence of Schizophrenia
AUDIT	Alcohol Use Disorders Identification Test
BA	Brodmann Areas
BDNF	Brain-Derived Neurotrophic Factor
BFRT	Benton Facial Recognition Test
BL	Baseline Assessment, Age 14
BOLD	Blood-Oxygen-Level-Dependent Signal
BPAD	Bipolar Affective Disorder
BPRS	Brief Psychiatric Rating Scale
CAARMS	Comprehensive Assessment of At-Risk Mental State
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAPE	Community Assessment of Psychic Experience Questionnaire
CASH	Comprehensive Assessment of Symptoms and History
CFA	Confirmatory Factor Analysis
CGT	Cambridge Guessing Task
CNV	Copy Number Variation
COMED	Continuum of Mental Disorders Study
COMT	Catechol-O-Methyltransferase
COS	Childhood Onset Schizophrenia
CT	Childhood Trauma
DAT	Dopamine Transporter Gene
DAST	Drug Abuse Screening Test
DCM	Dynamic Causal Modelling
DDA	Discarded/Disabled Acquisitions, Dummy Cycles
dF	Degrees of Freedom
DFC	Distance from Centre
DLPFC	Dorsolateral Prefrontal Cortex, including the Superior and Middle Frontal Gyri
DTI	Diffusion Tensor Imaging (white matter tractography)
DZ	Dizygotic
EDSP	Early Developmental Stages of Psychopathology Study
EEG	Electroencephalography

EFA	Exploratory Factor Analysis
EFTS	East Flanders Prospective Twin Survey
EHRS	Edinburg High Risk Study
EPI	Echo-Planar Imaging
EPPS	European Prediction of Psychosis Study
ERP	Event-Related Potential
ESEM	Exploratory Structural Equation Models
ESM	Experience Sampling Method
ETL	Echo Train Length
EVDT	Emotional Valence Discrimination Task
FA	Fractional Anisotropy
FEP	First Episode Psychosis
FEPSY	Basel Early Detection of Psychosis Study
FFM	Five Factor Model
FWE	Family Wise Error
FFA	Fusiform Face Area
FL	Frontal Lobe
fMRI	Functional Magnetic Resonance Imaging
FOV	Field-of-View
FT	Faces Task
FU	Follow-up Assessment, Age 19
FWHM	Full Width and Half Maximum
GAF	Global Assessment of Functioning
GLM	General Linear Model
GM	Gray Matter
GMD	Gray Matter Density
GMV	Gray Matter Volume
GNPS	Greek National Perinatal Survey
GROUP	Genetic Risk and Outcome of Psychosis
GWAS	Genome Wide Association Study
HBSC	Health Behaviour in School-Aged Children Study
HLA	Human Leucocyte Antigen
HPA	Hypothalamus-Pituitary-Adrenal Axis
HRF	Haemodynamic Response Function
IQ	Intelligence Quotient
IMAGEN	European research project examining how biological, psychological, and environmental factors during adolescence may influence brain development and mental health
LSHS	Launay-Slade Hallucination Scale
MHC	Major Histocompatibility Region
MID	Monetary Incentive Delay Task
MNI	Montreal Neurological Institute Space
MSI	Multisensory Integration
MTHFR	Folate-Regulating Methylenetetrahydrofolate Reductase
MZ	Monozygotic
NA	Nucleus Accumbens
NAPLS	North American Prodromal Longitudinal Study

NEMESIS	The Netherlands Mental Health Survey and Incidence Study
NEO FFI	Neuroticism-Extraversion-Openness Five-Factor Inventory
NRGN	Neurogranin
NSA	Number of Signal Averages
OR	Odds Ratio
PACE	Personal Assessment and Crisis Evaluation Clinic (Melbourne, Australia)
PANSS	Positive and Negative Syndrome Scale
PAS	Perceptual Aberration Scale
PDI	Peters et al. Delusional Inventory
PE	Psychotic Experiences
PFC	Prefrontal Cortex
PL	Parietal Lobe
PLE	Psychotic-Like Experiences
PPV	Positive Predictive Value
PRT	The Response Bias Probabilistic Rewards Task
ROC	Receiver Operating Characteristics
ROI	Region of Interest
SAT	Salience Attribution Test
SCAN	Schedule for Clinical Assessment in Neuropsychiatry
SCID	Structured Clinical Interview for DSM Disorders
SCL-90	Symptom Checklist
SCZ	Schizophrenia
SE	Standard Error
SIPS	Structured Interview for Prodromal Syndromes
SIS-R	Structured Interview for Schizotypy
sMRI	Structural Magnetic Resonance Imaging
SN	Substantia Nigra
SNP	Single Nucleotide Polymorphism
SPM	Statistical Parametric Mapping (Institute of Neurology, UCL)
SPQ	Schizotypal Personality Questionnaire
STS	Superior Temporal Sulcus
Sx	Symptoms
TCF4	Transcription Factor 4
TE	Echo Time
TL	Temporal Lobe
TPS	Transient Psychosis Syndrome
TR	Repetition Time
TRAILS	Tracking Adolescents' Individual Lives Survey
UHR	Ultra-High Risk (for psychosis)
VBM	Voxel-Based Morphometry
VLPFC	Ventrolateral Prefrontal Cortex, including the Middle and Inferior Frontal Gyri
VMPFC	Ventromedial Prefrontal Cortex
VS	Ventral Striatum
VTA	Ventral Tagmental Area
WISC	Wechsler Intelligence Battery for children
WM	White Matter

WMV	White Matter Volume
WM	Working Memory
ZNF804A	Zinc Finger Binding Protein 804A

Appendices

List of Appendices

APPENDIX I: CAPE-42 Worksheet

If *sometimes, often or nearly always* in column A, go to column B. If *never* in column A, go straight to the next question in column.

	Column A				Column B			
	Do you have a specific feeling, thought or mental experience?				How distressed are you by this experience?			
	Never	Sometimes	Often	Nearly Always	Not distressed	A bit distressed	Quite distressed	Very distressed
1) Do you ever feel sad?	0	1	2	3	1	2	3	4
2) Do you ever feel as if people seem to drop hints about you or say things with a double meaning?	0	1	2	3	1	2	3	4
3) Do you ever feel that you are not a very animated person?	0	1	2	3	1	2	3	4
4) Do you ever feel that you are not much of a talker when you are conversing with other people?	0	1	2	3	1	2	3	4
5) Do you ever feel as if things in magazines or on TV were written especially for you?	0	1	2	3	1	2	3	4
6) Do you ever feel as if some people are not what they seemed to be?	0	1	2	3	1	2	3	4
7) Do you ever feel as if you are being persecuted in some way?	0	1	2	3	1	2	3	4
8) Do you ever feel that you experience few or no emotions at important events?	0	1	2	3	1	2	3	4
9) Do you ever feel pessimistic about everything?	0	1	2	3	1	2	3	4
10) Do you ever feel as if there is a conspiracy against you?	0	1	2	3	1	2	3	4
11) Do you ever feel as if you are destined to be someone very important?	0	1	2	3	1	2	3	4
12) Do you ever feel as if there is no future for you?	0	1	2	3	1	2	3	4
13) Do you ever feel that you are a very special or unusual person?	0	1	2	3	1	2	3	4
14) Do you ever feel as if you do not want to live anymore?	0	1	2	3	1	2	3	4
15) Do you ever think that people can communicate telepathically?	0	1	2	3	1	2	3	4
16) Do you ever feel that you have no interest in being with other people?	0	1	2	3	1	2	3	4
17) Do you ever feel as if electrical devices such as computers can influence the way you think?	0	1	2	3	1	2	3	4
18) Do you ever feel you are lacking motivation to do things?	0	1	2	3	1	2	3	4
19) Do you ever cry about nothing?	0	1	2	3	1	2	3	4
20) Do you believe in the power of witchcraft, voodoo or the occult?	0	1	2	3	1	2	3	4

21) Do you ever feel that you are lacking in energy?	0	1	2	3	1	2	3	4
22) Do you ever feel that people are looking at you oddly?	0	1	2	3	1	2	3	4
23) Do you ever feel that your mind is empty?	0	1	2	3	1	2	3	4
24) Do you ever feel as if the thoughts in your head are being taken away from you?	0	1	2	3	1	2	3	4
25) Do you ever feel that you are spending your days doing nothing?	0	1	2	3	1	2	3	4
26) Do you ever feel as if the thoughts in your head are not your own?	0	1	2	3	1	2	3	4
27) Do you ever feel that your feelings are lacking in intensity?	0	1	2	3	1	2	3	4
28) Have your thoughts ever been so vivid that you are worried other people would hear them?	0	1	2	3	1	2	3	4
29) Do you ever feel you are lacking in spontaneity?	0	1	2	3	1	2	3	4
30) Do you ever hear your own thoughts echoed back to you?	0	1	2	3	1	2	3	4
31) Do you ever feel as if you are under the control of some force or power other than yourself?	0	1	2	3	1	2	3	4
32) Do you ever feel that your emotions are blunted?	0	1	2	3	1	2	3	4
33) Do you ever hear voices when you are alone?	0	1	2	3	1	2	3	4
34) Do you hear voices talking to each other when you are alone?	0	1	2	3	1	2	3	4
35) Do you ever feel that you are neglecting your appearance or personal hygiene?	0	1	2	3	1	2	3	4
36) Do you ever feel that you never get things done?	0	1	2	3	1	2	3	4
37) Do you feel that you have only few hobbies or interests?	0	1	2	3	1	2	3	4
38) Do you ever feel guilty?	0	1	2	3	1	2	3	4
39) Do you ever feel like a failure?	0	1	2	3	1	2	3	4
40) Do you ever feel tense?	0	1	2	3	1	2	3	4
41) Do you ever feel as if a double has taken the place of a family member, friend or acquaintance?	0	1	2	3	1	2	3	4
42) Do you ever see objects, people or animals that other people cannot see?	0	1	2	3	1	2	3	4

APPENDIX II: fMRI differences between SCZ patients and controls.

BA	Face task [189,192-194,196,197]	Reward Task [202,205-212]
1		
2		
3		
4		
5		
6	Precentral Gyrus, Frontal Lobe	
7	Superior Parietal Lobule, Parietal Lobe	
8		
9	Precentral Gyrus, Frontal Lobe	Medial Frontal Gyrus, Frontal Lobe
10		Medial Frontal Gyrus, Frontal Lobe
11		Medial Frontal Gyrus, Frontal Lobe
12		
13	Insula, Sub-lobar	
14		
15		
16		
17		
18	Cuneus, Occipital Lobe, Precuneus, Parietal Lobe	
19	Lingual Gyrus, Occipital Lobe	Middle Occipital Gyrus, Occipital Lobe
20		Inferior Temporal Gyrus, Temporal Lobe
21	Superior Temporal Gyrus, Temporal Lobe	Superior Temporal Gyrus, Temporal Lobe
22	Superior/Middle Temporal Gyrus, Temporal Lobe	Middle Temporal Gyrus, Temporal Lobe
23		
24	Cingulate Gyrus, Limbic Lobe	Cingulate Gyrus, Limbic Lobe
25		
26		
27	Parahippocampal Gyrus, Limbic Lobe	
28	Parahippocampal Gyrus, Limbic Lobe	
29	Posterior Cingulate Gyrus, Limbic Lobe	
30		Posterior Cingulate Gyrus, Limbic Lobe
31	Precuneus, Parietal Lobe	Cingulate Gyrus, Limbic Lobe
32	Cingulate Gyrus, Limbic Lobe	Cingulate Gyrus, Limbic Lobe
33		
34	Parahippocampal Gyrus/Uncus, Limbic Lobe	Subcallosal Gyrus, Frontal Lobe
35	Parahippocampal Gyrus, Limbic Lobe	
36	Parahippocampal Gyrus, Limbic Lobe	
37	Sub-gyral, Temporal Lobe	Middle Temporal Gyrus, Temporal Lobe
38	Superior Temporal Gyrus, Temporal Lobe	Superior Temporal Gyrus, Temporal Lobe
39	Middle Temporal Gyrus, Temporal Lobe	
40	Inferior Parietal Lobule, Parietal Lobe	Inferior Parietal Lobule, Parietal Lobe
41		Superior Temporal Gyrus, Temporal Lobe
42		
43		
44	Inferior Frontal Gyrus, Frontal Lobe	
45		
46		
47	Inferior Frontal Gyrus, Frontal Lobe	Inferior Frontal Gyrus, Frontal Lobe
48		
49		
50		
51		
52		
	Amygdala Putamen/Globus Pallidus, Lentiform Nucleus Caudate Head/Body	Putamen/Globus Pallidus, Lentiform Nucleus Caudate Head Pulvinar Nuclei, Thalamus Mammilary Body

APPENDIX III: Growth changes during normal brain development.

BA	Childhood to Adolescence Positive DFC Difference [216]	Childhood to Adolescence Negative DFC Difference [216]	Adolescence to Adulthood Positive DFC Difference [216]	Adolescence to Adulthood Negative DFC Difference [216]	Child>Adolescent Largest Clusters [218]	Adolescent>Adult Largest Clusters [217]
1		Postcentral G.				
2				Postcentral G.		
3						
4				Precentral G.		
5		Postcentral G.		Postcentral G.	Postcentral G.	
6	Precentral G.	Superior Frontal G.	Superior Frontal G.	Precentral G.	Superior Frontal G.	Superior Frontal G.
7	Postcentral G.	Superior Par. Lob.		Postcentral G.	Superior Par. Lob.	
8	Middle Frontal G.	Superior Frontal G.	Middle Frontal G.	Middle Frontal G.		Superior Frontal G.
9	Superior Frontal G.	Superior Frontal G.	Superior Frontal G.	Superior Frontal G.		
10		Superior Frontal G.	Middle Frontal G.			
11	Inferior Frontal G.	Superior Frontal G.	Superior Frontal G.			
12						
13						Insula, Sub-lobar
14						
15						
16						
17						
18	Cuneus, Occipital L,			Cuneus, Limbic L.		
19	Cuneus, Precuneus	Middle Temporal G.	Fusiform G.	Precuneus, Limbic L.		
20	Inferior Temp. G.		Inferior Temporal G.			
21			Middle Temporal G.			
22	Superior Temp. G.		Superior Temp. G.	Superior Temp. G.		Superior Temp. G.
23						
24						
25						
26						
27						
28						
29						
30						
31					Cingulate Gyrus	
32						
33						
34						
35						
36						
37					Fusiform Gyrus	
38		Superior Temporal G.				
39		Middle Temporal G.				
40		Inferior Parietal Lob.	Inferior Parietal Lob.	Inferior Parietal Lob.		
41						
42						
43						
44						
45				Inferior Frontal G.		
46	Inferior Frontal G.			Inferior Frontal G.		
47	Middle Frontal G.		Orbital G., Frontal L.	Middle Frontal G.		
48						
49						
50						
51						
52						Globus Pallidus

Abbreviations

BA: Brodmann Area: **DFC:** Distance from Centre; **G.**: Gyrus; **L.**: Lobe; **Lob.**: Lobule

APPENDIX IV: The Edinburgh High Risk Study, Gray Matter changes in Psychosis.

BA	FEP>CTR (GMD) [219]	UHR>FEP (GMD) [220]	CTR>UHR (GMD) [220]	UHR+TPS>UHR (GMD ↓ in 2y) [221,222]	UHR+TPS+SCZ > UHR+TPS (GMD ↓ in 2y) [221,222]
1					
2					
3					
4					
5					
6					
7					
8					
9		Medial Frontal G.			
10		Medial Frontal G.			
11	Medial Frontal G.				
12					
13	Super. Temporal G.				
14					
15					
16					
17					
18					
19					
20				Inferior Temporal G.	Inferior Temporal G.
21	Middle Temporal G.				
22		Middle Temporal G.		Super. Temporal G.	
23					
24					
25					
26					
27					
28	Uncus, Limbic Lobe				Uncus, Limbic Lobe
29					
30					
31					
32	Anter. Cingulate G.	Anter. Cingulate G.	Anter. Cingulate G.		
33					
34	Subcallosal Gyrus	Parahippocampal G.	Parahippocampal G.		
35	Parahippocampal G.	Parahippocampal G.			
36				Uncus, Limbic Lobe	
37					
38					
39		Middle Temporal G.			
40		Postcentral G.			
41	Super. Temporal G.				
42					
43	Postcentral G.				
44		Precentral G.			
45		Inferior Frontal G.			
46					
47		Inferior Frontal G.			
48					
49					
50					
51					
52					
	Amygdala	Amygdala Hippocampus		Caudate Tail	

Abbreviations

BA: Brodmann Area; **CTR:** Controls; **FEP:** First Episode Psychosis; **GMD:** Gray Matter Density; **G.**: Gyrus; **SCZ:** Schizophrenia, developed later; **TPS:** Transient Psychosis Syndrome; **UHR**: Ultra-High Risk for Psychosis

APPENDIX V: IMAGEN fMRI Acquisition Parameters

Sequence Parameter	Value
No. of Volumes	191 (MID), 202 (FT)
TR (ms)	2200
TE (ms)	30
ETL	32
NSA	1
Excitation flip angle (degrees)	75
2D/3D	2D
Voxel Size (mm)	3.4 x 3.4 x 2.4
Matrix size	64^2
No. of slices/DDAs	40/3
FOV frequency (mm)	218
FOV phase (%)	100%
Slice thickness (mm)	2.4
Slice gap (mm)	3.4
Slice orientation	Oblique (ACPC)
In-plane phase encode direction	Anterior-Posterior
Slice acquisition order	Sequential
Slice acquisition direction	Superior-Inferior

Abbreviations

TR: Repetition Time; **TE:** Echo Time; **ETL:** Echo Train Length; **NSA:** Number of Signal Averages (average number for each phase encoding step); **DDA:** Discarded or Disabled Acquisitions, Dummy Cycles; **FOV:** Field of View; **ACPC:** Anterior Commissure-Posterior Commissure Plane

APPENDIX VI: Correlations between selected CAPE scores, Overall Sample

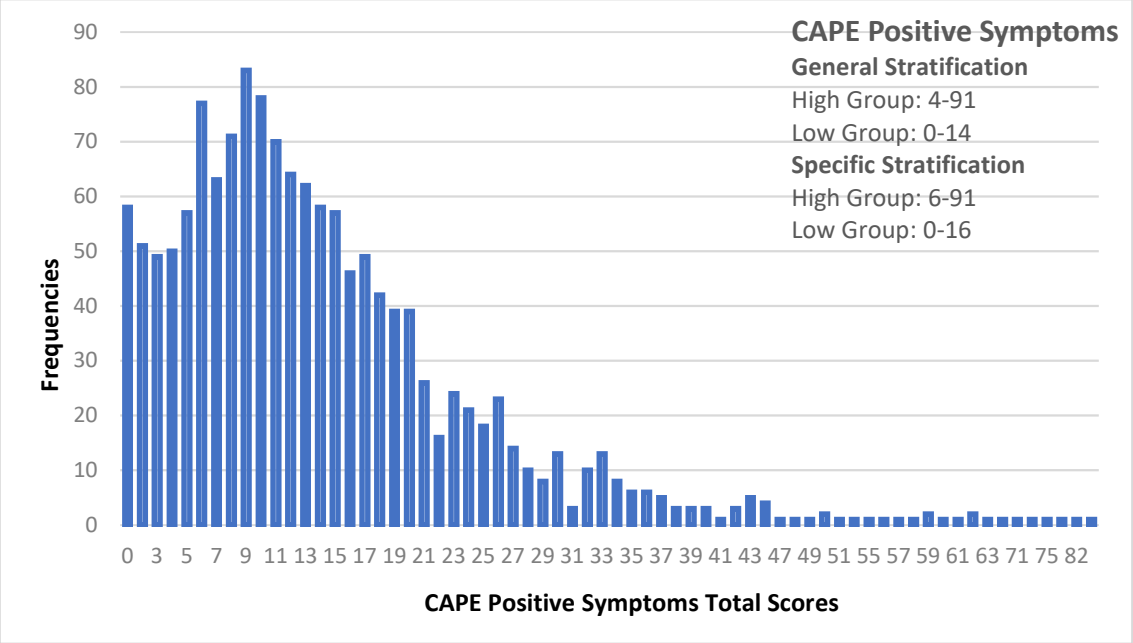
	CAPE Grand Total	CAPE Positive Symptoms Total	CAPE Bizarre Delusions Total	CAPE Social Delusions Total	CAPE Negative Symptoms Total	CAPE 3-Items Total
CAPE Grand Total	1.000	**0.790** (p<0.0001)	**0.558** (p<0.0001)	**0.761** (p<0.0001)	**0.913** (p<0.0001)	**0.510** (p<0.0001)
CAPE Positive Symptoms Total	**0.790** (p<0.0001)	1.000	**0.755** (p<0.0001)	**0.931** (p<0.0001)	**0.584** (p<0.0001)	**0.643** (p<0.0001)
CAPE Bizarre Delusions Total	**0.558** (p<0.0001)	**0.755** (p<0.0001)	1.000	**0.497** (p<0.0001)	**0.405** (p<0.0001)	**0.578** (p<0.0001)
CAPE Social Delusions Total	**0.761** (p<0.0001)	**0.931** (p<0.0001)	**0.497** (p<0.0001)	1.000	**0.567** (p<0.0001)	**0.563** (p<0.0001)
CAPE Negative Symptoms Total	**0.913** (p<0.0001)	**0.584** (p<0.0001)	**0.405** (p<0.0001)	**0.567** (p<0.0001)	1.000	**0.364** (p<0.0001)
CAPE 3-Items Total	**0.510** (p<0.0001)	**0.643** (p<0.0001)	**0.578** (p<0.0001)	**0.563** (p<0.0001)	**0.364** (p<0.0001)	1.000

In bold: Spearman's rho (correlation coefficient), non-parametric
p: 2-tailed significance level

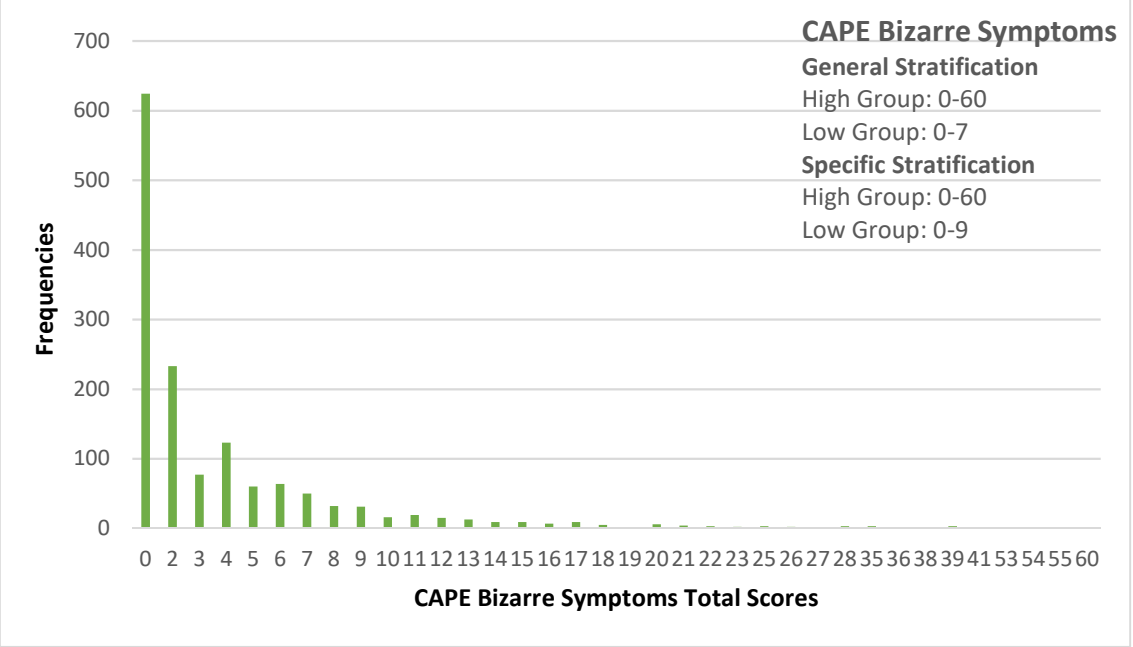
CAPE 3-items scores showed the weakest correlation with all other scores, including the CAPE grand total scores; these properties reinforced my choice of this composite measure in providing an alternative stratification method.

APPENDIX VII: Frequencies Histograms of selected CAPE scores, Overall Sample

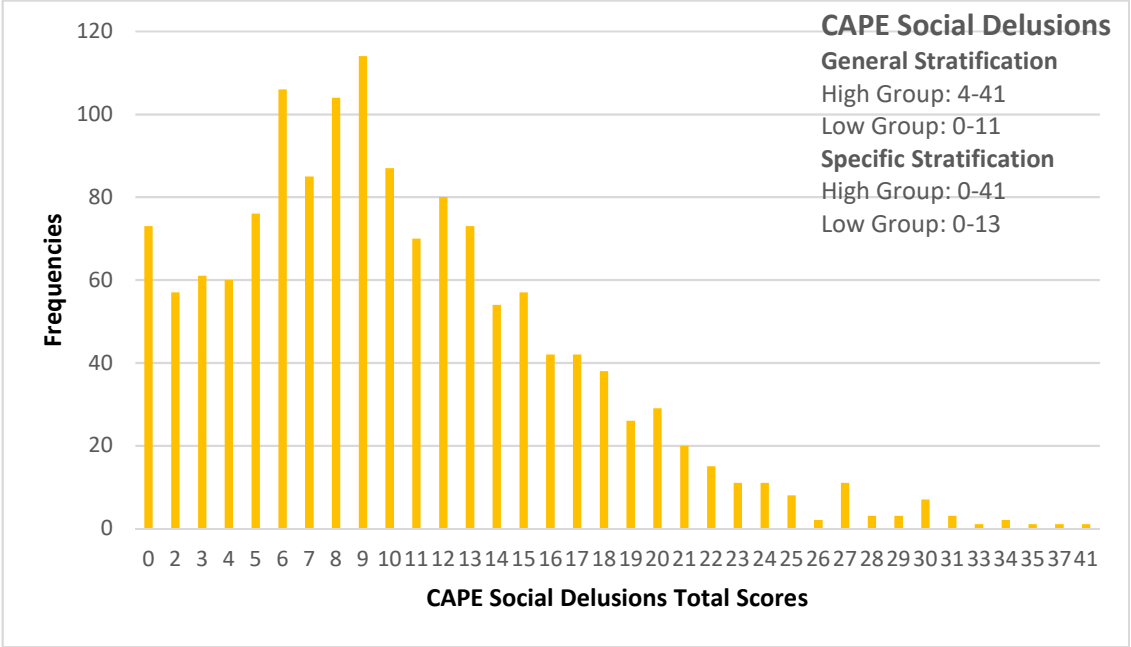
CAPE Positive Symptoms Total Scores Frequencies Histogram



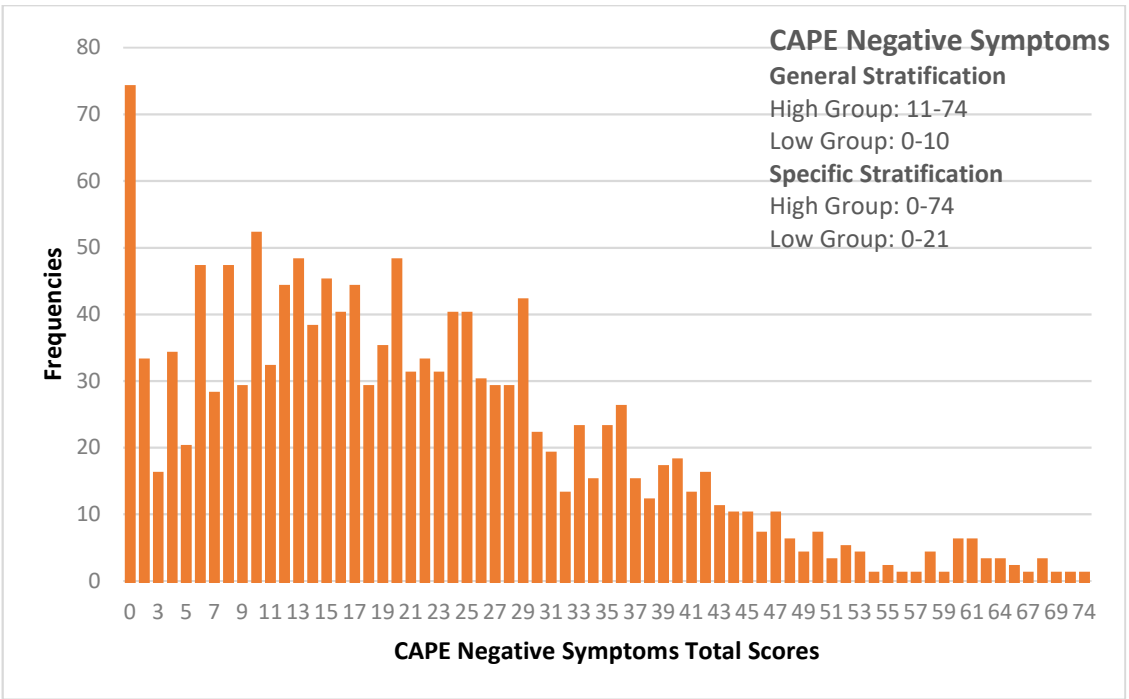
CAPE Bizarre Symptoms Total Scores Frequencies Histogram



CAPE Social Delusions Total Scores Frequencies Histogram



CAPE Negative Symptoms Total Scores Frequencies Histogram



APPENDIX VIII: CANTAB Affective Go-NoGo Task (AGN)

Overview of AGN Task

Administration time: Around 10 minutes, depending on level of impairment. The modified IMAGEN version lasts approximately 8 minutes.

Task: The test consists of several blocks, each of which presents a series of words from two of three different Affective categories: positive (e.g. joyful), anxiety-related (e.g. attack), depression-related (e.g. useless) and neutral (e.g. element). The subject is given a target category, as is asked to press the pad when they see a word matching this category.

Test modes: Six modes. Four using positive and negative stimuli only, two using positive, negative and neutral stimuli. The affective Go-NoGo task was supplemented by anxiety-related words in Mannheim and the total number of blocks were reduced to shorten the task. IMAGEN used this modified mode including positive, anxiety-related and depression-related and neutral stimuli.

Outcome measures: Several measures covering latency and errors of commission and omission.

AGN Outcome Measures

AGN Mean correct latency (positive): Average reaction time for correctly identified positive stimuli.

AGN Mean correct latency (negative): Average reaction time for correctly identified negative stimuli.

AGN Mean correct latency (neutral): Average reaction time for correctly identified neutral stimuli.

AGN Total commissions (positive): Number of responses to distractors for positive stimuli.

AGN Total commissions (negative): Number of responses to distractors for negative stimuli.

AGN Total commissions (neutral): Number of responses to distractors for neutral stimuli.

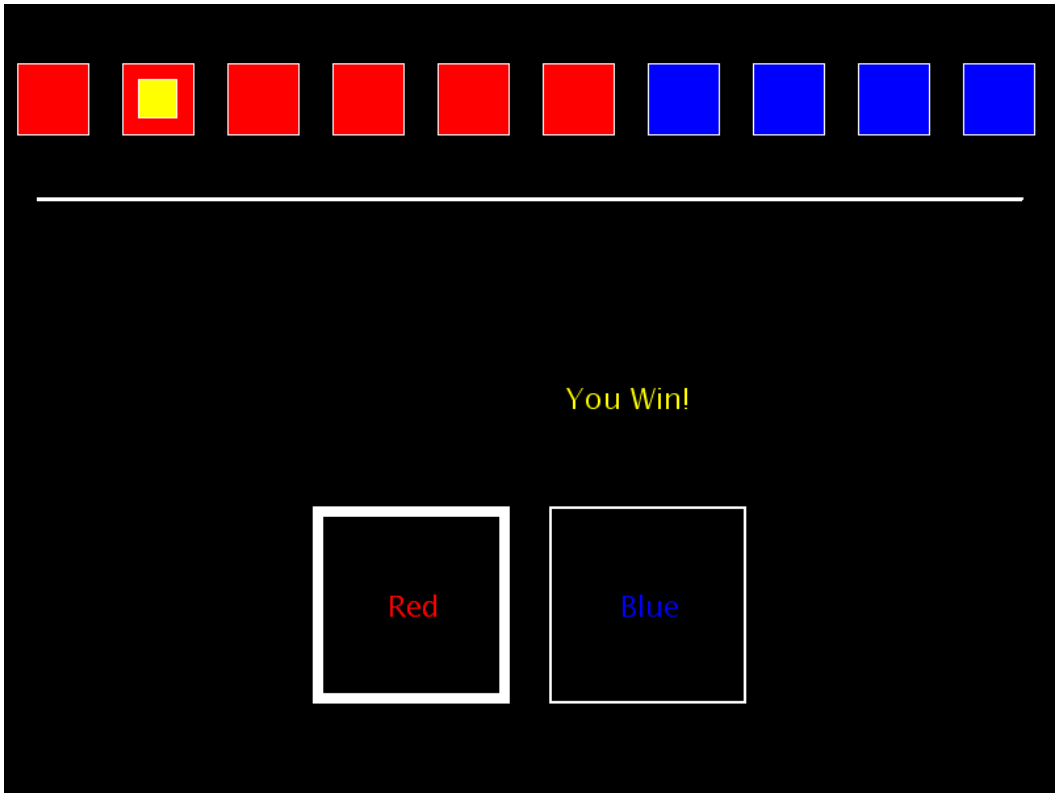
AGN Total omissions (positive): Number of missed responses for positive stimuli.

AGN Total omissions (negative): Number of missed responses for negative stimuli.

AGN Total omissions (neutral): Number of missed responses for neutral stimuli.

APPENDIX IX: CANTAB Cambridge Guessing Task (CGT)

Overview of CGT Task



Administration time: Up to 30 minutes.; The modified IMAGEN version lasts approximately 15-20 minutes.

Task: On each trial, the subject is presented with a row of ten boxes across the top of the screen, some of which are red and some of which are blue. At the bottom of the screen are rectangles containing the words 'Red' and 'Blue'. The subject must guess whether a yellow token is hidden in a red or a blue box. In the gambling stages, subjects start with a number of points, displayed on the screen, and can select a proportion of these points, displayed in either rising or falling order, in a second box on the screen, to gamble on the confidence they have in their decision. A stake box on the screen displays the current amount of the bet. The subject must try to accumulate as many points as possible.

Test modes: Ascending first (where stakes are displayed in ascending order for two stages, then in descending order for two stages) and Descending first (where stakes are displayed in descending order for two stages, then in ascending order for two stages). IMAGEN used a modified version in which the time between stakes is reduced from 5s to 2s to make the task shorter and more interesting for adolescents.

Outcome measures: Several measures cover risk taking, quality of decision making, deliberation time, risk adjustment, delay aversion and overall proportion bet.

CGT Outcome Measures

CGT Delay aversion: Tendency to bet larger amounts when possible bet amounts are presented in descending order (calculated by subtracting risk taking measure from ascending trials from risk taking measure of descending trials).

CGT Deliberation time: Mean latency from presentation of coloured boxes to subject's choice of which colour to bet on.

CGT Overall proportion bet: Average proportion of the current point total (using nominal percentage) that subject is willing to risk on each gamble test trial.

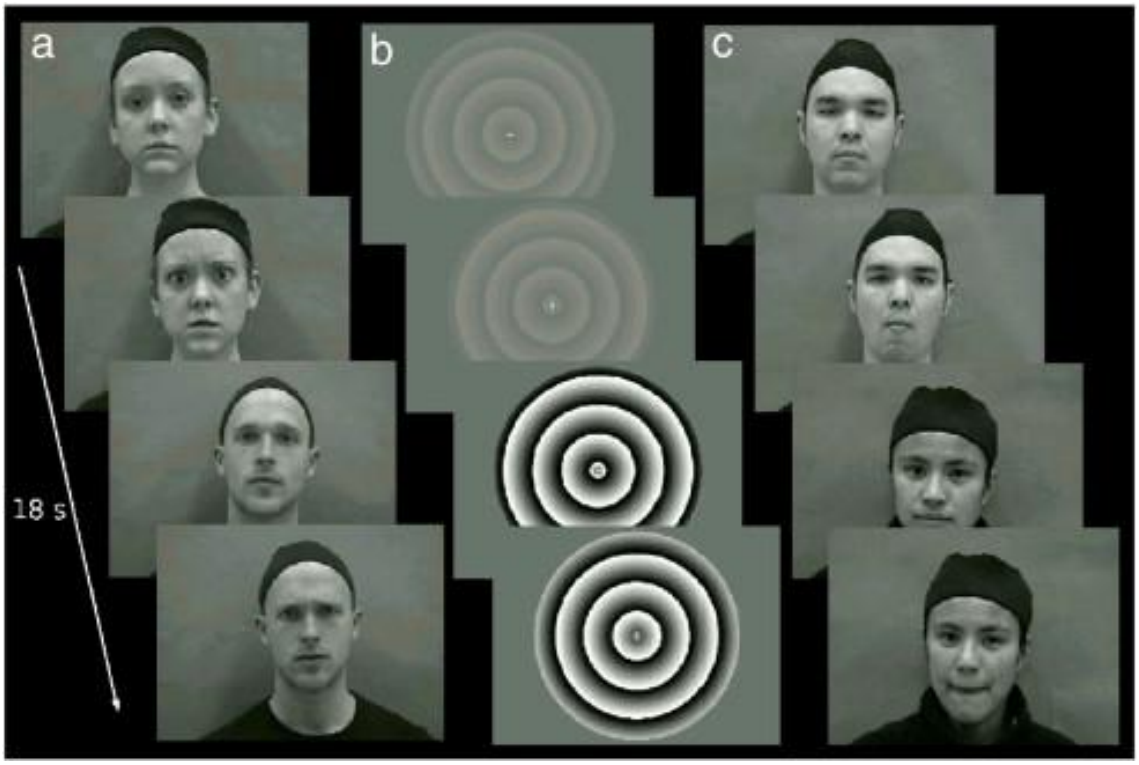
CGT Quality of decision making: Proportion of test trials on which the subject bets on the more likely outcome of the two choices.

CGT Risk adjustment: Tendency to bet higher proportion of points when the large majority of boxes are the colour chosen.

CGT Risk taking: Mean proportion of the current points total that subject is willing to risk on trial for which they have chosen the more likely outcome.

APPENDIX X: The Faces Task

Blocks of videos showing faces neutral and angry faces. Faces that turn from neutral to angry (a) or stay neutral (c) are interspersed with blocks of control stimuli (b) [228].



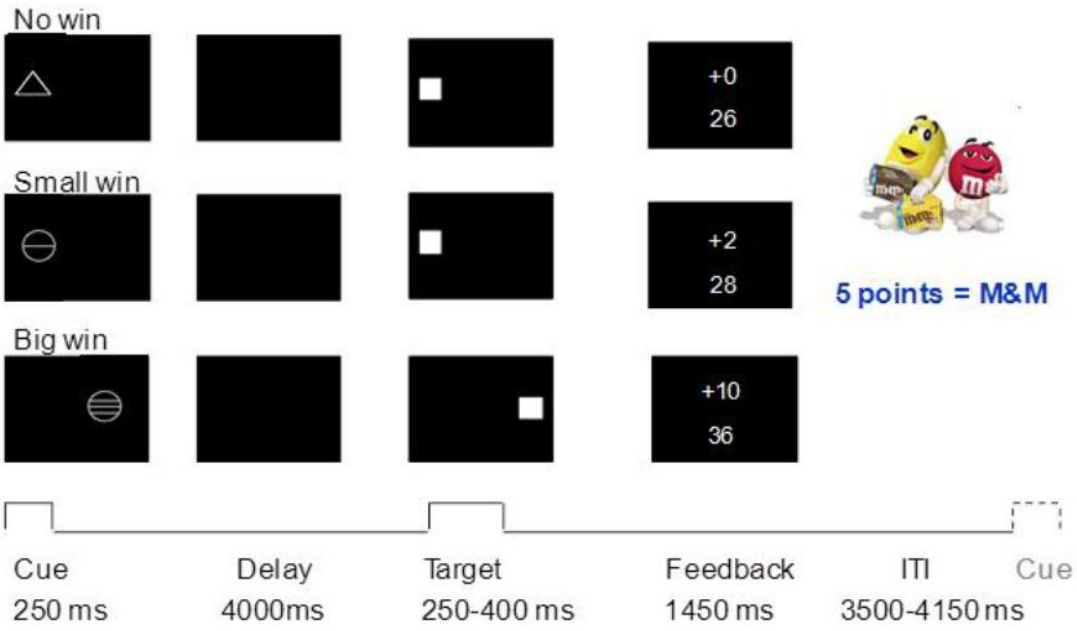
Instructions in English

In the following scanning session, we will ask you to perform different tasks and games which are so far unfamiliar to you. Therefore, we would like to explain these tasks and games first outside the scanner using this standard computer. Additionally, you have the opportunity to practice some of the tasks. Let's start with a few simple tasks which target basic functions of the brain.

In this task you will be presented with short video clips showing faces with neutral and angry expressions as well as moving circles. Please watch them carefully and remember to lie as still as possible during this task.

APPENDIX XI: The Monetary Incentive Delay Task

Outline of the stages of the MID Task.



Instructions in English

In the following scanning session, we will ask you to perform different tasks and games which are so far unfamiliar to you. Therefore, we would like to explain these tasks and games first outside the scanner using this standard computer. Additionally, you have the opportunity to practice some of the tasks. Let's start with a few simple tasks which target basic functions of the brain.

This task is a reaction time task - it tests how quickly you can press the button to hit a target, which is a white square appearing only for a short time on the left or right of the screen. If you manage to press the button as soon as the white square appears, you will score points. If you respond too early (before the white square appears) or too late (after the white square has disappeared) you will not gain any points. You can tell where the white square will appear and how many points you will win by the symbol you see on the screen before the white square is shown. A triangular symbol means you will not win any points, a circle with a line means you will win 2 points and a circle with three lines means you will win 10 points. You should try to win as many points as you can! - but only if you press the button while the square is presented on the screen! For every 5 points you win, you will receive an M&M, see how many you can win!

APPENDIX XII: Epidemiological Characteristics of CAPE General Stratification Samples

	CAPE GRAND TOTAL UPPER 10% (n=149)						CAPE GRAND TOTAL LOWER 10% (n=149)					
	Min	**Max**	**Mean**	**SE**	**SD**	**Var**	**Min**	**Max**	**Mean**	**SE**	**SD**	**Var**
GENDER (Male %)			33.60%						56.40%			
HANDEDNESS (R %)			85.90%						82.60%			
AGE BL (y)	13.36	15.61	14.47	0.03	0.39	0.15	12.73	15.32	14.43	0.03	0.38	0.15
AGE FU2 (y)	17.82	21.44	19.02	0.06	0.76	0.58	16.82	21.47	18.98	0.06	0.74	0.55
WISC VERBAL SCORE (BL)	59	155	111.15	1.32	15.66	245.14	71	146	106.72	1.28	15.24	232.36
WISC PERFORMANCE SCORE (BL)	73	147	108.49	1.33	15.79	249.31	63	149	105.20	1.20	14.42	208.02
ADRS TOTAL SCORE (FU)	10	20	15.89	0.24	2.96	8.74	16	20	19.70	0.06	0.72	0.52
AUDIT TOTAL SCORE (FU)	0	26	7.5	0.44	5.34	28.52	0	21	5.26	0.32	3.87	14.97
DAST CANNABIS TOTAL SCORE (FU)	0	11	1.59	0.21	2.52	6.37	0	4	0.54	0.08	1.02	1.03
CAPE GRAND TOTAL SCORE (FU)	91	182	111.64	1.74	21.26	451.95	0	16	9.54	0.39	4.75	22.55
CAPE POSITIVE SYMPTOMS TOTAL SCORE (FU)	4	91	33.09	1.27	15.48	239.68	0	14	3.23	0.24	2.98	8.86
CAPE BIZARRE DELUSIONS TOTAL SCORE (FU)	0	60	13.17	0.97	11.83	139.85	0	7	0.37	0.09	1.09	1.18
CAPE SOCIAL DELUSIONS TOTAL SCORE (FU)	4	41	19.91	0.54	6.57	43.11	0	11	2.87	0.21	2.61	6.81
CAPE NEGATIVE SYMPTOMS TOTAL SCORE (FU)	11	74	46.37	0.93	11.37	129.19	0	10	2.22	0.21	2.61	6.80
CAPE DEPRESSIVE SYMPTOMS TOTAL SCORE (FU)	13	49	32.18	0.61	7.49	56.11	0	12	4.09	0.21	2.54	6.46
CAPE ITEMS [5 + 7 + 33] SCORE (FU)	0	16	4.73	0.28	3.46	12	0	4	0.15	0.05	0.60	0.36

Abbreviations

WISC: Wechsler Intelligence Batter for Children [223]; **ADRS:** Adolescent Depression Rating Scale [224]; **AUDIT:** Alcohol Use Disorders Identification Test [225]; **DAST:** Drug Abuse Screening Test [226]; **CAPE:** Community Assessment of Psychic Experiences Questionnaire [73]; **SD:** Standard Deviation; **SE:** Standard Error; **Var**: Variance

APPENDIX XIII: Epidemiological Characteristics of CAPE Specific Stratification Samples

	CAPE SPECIFIC ITEMS TOTAL UPPER 25% (n=366)						CAPE SPECIFIC ITEMS TOTAL LOWER 25% (n=330)					
	Min	**Max**	**Mean**	**SE**	**SD**	**Var**	**Min**	**Max**	**Mean**	**SE**	**SD**	**Var**
GENDER (Male %)			41.50%						55.50%			
HANDEDNESS (R %)			84.70%						83.90%			
AGE BL (y)	13.21	15.92	14.44	0.02	0.42	0.17	12.73	15.5	14.41	0.02	0.40	0.16
AGE FU2 (y)	17.75	21.53	18.99	0.04	0.75	0.56	16.82	21.9	18.97	0.04	0.75	0.56
WISC VERBAL SCORE (BL)	59	155	111.12	0.86	15.84	250.83	71	150	109.37	0.86	15.12	228.55
WISC PERFORMANCE SCORE (BL)	69	147	108.29	0.82	15.22	231.53	63	149	106.40	0.88	15.39	236.76
ADRS TOTAL SCORE (FU)	10	20	17.88	0.14	2.62	6.87	16	20	19.68	0.04	0.73	0.54
AUDIT TOTAL SCORE (FU)	0	26	6.00	0.24	4.51	20.33	0	27	5.47	0.24	4.38	19.17
DAST CANNABIS TOTAL SCORE (FU)	0	11	1.12	0.11	2.13	4.54	0	7	0.58	0.07	1.20	1.44
CAPE GRAND TOTAL SCORE (FU)	15	182	76.21	1.67	31.97	1021.99	0	29	17.35	0.44	7.98	63.63
CAPE POSITIVE SYMPTOMS TOTAL SCORE (FU)	6	91	25.14	0.70	13.30	176.95	0	16	4.90	0.20	3.59	12.91
CAPE BIZARRE DELUSIONS TOTAL SCORE (FU)	0	60	8.39	0.48	9.26	85.71	0	9	0.58	0.07	1.33	1.77
CAPE SOCIAL DELUSIONS TOTAL SCORE (FU)	0	41	16.75	0.33	6.40	40.93	0	13	4.32	0.18	3.21	10.32
CAPE NEGATIVE SYMPTOMS TOTAL SCORE (FU)	0	74	29.59	0.78	14.82	219.72	0	21	6.19	0.26	4.77	22.75
CAPE DEPRESSIVE SYMPTOMS TOTAL SCORE (FU)	0	47	21.48	0.53	10.06	101.10	0	18	6.26	0.20	3.57	12.72
CAPE ITEMS [5 + 7 + 33] SCORE (FU)	3	16	4.86	0.11	2.15	4.63	0	0	0	0	0	0

Abbreviations

WISC: Wechsler Intelligence Batter for Children [223]; **ADRS:** Adolescent Depression Rating Scale [224]; **AUDIT:** Alcohol Use Disorders Identification Test [225]; **DAST:** Drug Abuse Screening Test [226]; **CAPE:** Community Assessment of Psychic Experiences Questionnaire [73]; **SD:** Standard Deviation; **SE:** Standard Error; **Var**: Variance

APPENDIX XIV: FT Study, fROI Brain Analysis, Tables of Results

Appendix XIV: General Stratification

FT Study, fROI Brain Analysis, CAPE General Stratification

Time-Point	Contrast	Analysis	MNI coordinates			Anatomical Area	K	p(FEW-corr) Cluster Level	p(FEW-corr) Peak Level	T score	Z score
			X	Y	Z						
BL	Angry-Control	High>Low	42	8	-14	Right Insular Cortex, BA13	2	0.007*	0.016*	5.19	5.06
FU	Angry-Control	Group Average Positive	-12	5	10	Left Caudate Body	7	<0.0001	0.001	5.73	5.56
FU	Angry-Control	Group Average Positive	6	65	31	Right Frontal Lobe, Superior Frontal Gyrus, BA10	99	<0.0001	<0.0001	7.82	7.39
FU	Angry-Control	Group Average Negative	33	-46	-5	Right Limbic Cortex, Parahippocampal Gyrus, BA19	12543	NaN	<0.0001	16.77	Inf

Abbreviations

BL: Baseline; **FU:** Follow-up; **High Group**: Scorers in upper 10% of CAPE Total Score, n=149; **Low Group:** Scorers in lower 10% CAPE Total Score, n=149; **High>Low:** showing increased activation in the High but not in the Low Group; **Low>High:** showing increased activation in the Low but not in the High Group; **Group Average Positive:** showing increased activation in both High and Low Groups; **Group Average Negative:** showing decreased activation in both High and Low Groups; **BA:** Brodmann Area; **K:** number of Voxels; **p(FWE-corr):** p value corrected for Family Wise Error (false positives); **NaN:** Not a Number; **Inf:** Infimum; **(*):** did not survive Bonferoni correction for multiple testing at p=0.00625.

Appendix XIV: Specific Stratification

FT Study, fROI Brain Analysis, CAPE Specific Stratification

Time-Point	Contrast	Analysis	MNI coordinates			Anatomical Area	K	p(FEW-corr) Cluster Level	p(FEW-corr) Peak Level	T score	Z score
			X	Y	Z						
BL	Angry-Control	Group Average Positive	-6	-73	-26	Left Cerebellum, Posterior Lobe, Declive	129	<0.0001	<0.0001	13.43	Inf
BL	Angry-Control	Group Average Negative	-33	11	10	Left Insular Cortex, BA13	4	0.002	0.003	5.42	5.35
FU	Angry-Control	Group Average Positive	-15	-40	-44	Left Cerebellum, Posterior Lobe, Tonsil	3	0.003	<0.0001	7.29	7.14
FU	Angry-Control	Group Average Negative	-33	17	-11	Left Insular Cortex, BA13	3	0.003	0.009*	5.2	5.14

Abbreviations

BL: Baseline; **FU:** Follow-up; **High Group**: Scorers in upper 25% of CAPE 3-Items Score, n=366; **Low Group:** Scorers in lower 25% CAPE 3-Items Score, n=330; **High>Low:** showing increased activation in the High but not in the Low Group; **Low>High:** showing increased activation in the Low but not in the High Group; **Group Average Positive:** showing increased activation in both High and Low Groups; **Group Average Negative:** showing decreased activation in both High and Low Groups; **BA:** Brodmann Area; **K:** number of Voxels; **p(FWE-corr):** p value corrected for Family Wise Error (false positives); **(*):** did not survive Bonferoni correction for multiple testing at p=0.00625.

APPENDIX XV: FT Study, Exploratory Cross-Sectional fROI Analysis, Tables of Results

Appendix XV: General Stratification

FT Study, Exploratory Cross-Sectional Analysis, Independent T-tests, CAPE General Stratification

Time-Point	MNI Coordinates			Anatomical Area	High Group Mean Brain Activation (Parameter Estimates)	Low Group Mean Brain Activation (Parameter Estimates)	Group Activation Relation	t-test for Equality of Means			
	X	Y	Z					t-test	df	Sig.	r
BL	42	8	-14	Right Insular Cortex, BA13	0.146	-0.269	H>L	5.188	264	<0.0001	0.304
FU	-12	5	10	Left Caudate Body	0.066	0.173	L>H	-2.588	255	0.01	0.160
FU	6	65	31	Right Frontal Lobe, Superior Frontal Gyrus, BA10	0.245	0.446	L>H	-2.283	257	0.023	0.141
FU	33	-46	-5	Right Limbic Cortex, Parahippocampal Gyrus, BA19	-0.458	-0.324	L>H	-2.85	255	0.005	0.176

Abbreviations

BL: Baseline; **FU:** Follow-up; **BA:** Brodmann Area; **H>L:** High Group showing more activation than Low Group; **L>H:** Low Group showing more activation than High Group; **r:** Pearson's correlation coefficient; **df:** degrees of Freedom

Appendix XV: Specific Stratification

FT Study, Exploratory Cross-Sectional Analysis, Independent T-tests, CAPE Specific Stratification

Time-Point	MNI Coordinates			Anatomical Area	High Group Mean Brain Activation (Parameter Estimates)	Low Group Mean Brain Activation (Parameter Estimates)	Group Activation Relation	t-test for Equality of Means			
	X	Y	Z					t-test	df	Sig.	r
BL	-6	-73	-26	Left Cerebellum, Posterior Lobe, Declive	0.24	0.156	H>L	2.828	619	0.005	0.113
BL	-33	11	10	Left Insular Cortex, BA13	-0.128	-0.052	L>H	-2.278	618	0.023	0.091
FU	-15	-40	-44	Left Cerebellum, Posterior Lobe, Tonsil	0.083	0.184	L>H	-2.75	603	0.006	0.111
FU	-33	17	-11	Left Insular Cortex, BA13	-0.122	-0.048	L>H	-2.275	596	0.023	0.093

Abbreviations

BL: Baseline; **FU:** Follow-up; **BA:** Brodmann Area; **H>L:** High Group showing more activation than Low Group; **L>H:** Low Group showing more activation than High Group; **r:** Pearson's correlation coefficient; **df:** degrees of Freedom

APPENDIX XVI: FT Study, Exploratory Longitudinal fROI Analysis, Tables of Results

Appendix XVI: General Stratification

FT Study, Exploratory Longitudinal Analysis, Paired T-tests, CAPE General Stratification

MNI Coordinates			Anatomical Area	Groups	Baseline Mean Brain Activation (Parameter Estimates)	Follow-up Mean Brain Activation (Parameter Estimates)	Group Activation Relation	t-test for Equality of Means			
X	Y	Z						t-test	df	Sig.	r
33	-46	-5	Right Limbic Cortex, Parahippocampal Gyrus, BA19	HIGH & LOW General	-0.267	-0.384	BL>FU	3.481	231	0.001	0.223
				HIGH General	-0.283	-0.456	BL>FU	4.307	116	<0.0001	0.371
				LOW General	-0.250	-0.311	BL>FU	1.129	114	0.261*	0.105
6	65	31	Right Frontal Lobe, Superior Frontal Gyrus, BA10	HIGH & LOW General	0.224	0.367	FU>BL	-2.614	231	0.01	0.169
				HIGH General	0.203	0.250	FU>BL	-0.579	116	0.564*	0.054
				LOW General	0.246	0.487	FU>BL	-3.311	114	0.001	0.296
42	8	-14	Right Insular Cortex, BA13	HIGH & LOW General	-0.065	-0.064	FU>BL	-0.017	231	0.987*	0.001
				HIGH General	0.157	-0.028	BL>FU	1.828	116	0.07*	0.167
				LOW General	-0.291	-0.1	FU>BL	-2.05	114	0.043	0.188

Abbreviations

BA: Brodmann Area; **BL>FU:** Baseline activation greater than Follow-up activation; **FU>BL:** Follow-up activation greater than Baseline activation; **r:** Pearson's correlation coefficient, **(*)**: not statistically significant at a p=0.05 level; **df:** degrees of Freedom.

High General: Scorers in upper 10% of CAPE Total Score, n=149; **Low General:** Scorers in lower 10% CAPE Total Score, n=149.

Appendix XVI: Specific Stratification

FT Study, Exploratory Longitudinal Analysis, Paired T-tests, CAPE Specific Stratification

MNI Coordinates			Anatomical Area	Groups	Baseline Mean Brain Activation (Parameter Estimates)	Follow-up Mean Brain Activation (Parameter Estimates)	Group Activation Relation	t-test for Equality of Means			
X	Y	Z						t-test	df	Sig.	r
-33	17	-11	Left Insular Cortex, BA13	HIGH & LOW Specific	-0.017	-0.083	BL>FU	2.795	550	0.005	0.118
				HIGH Specific	-0.026	-0.132	BL>FU	3.258	288	0.001	0.189
				LOW Specific	-0.007	-0.028	BL>FU	0.618	261	0.537*	0.038
-33	11	10	Left Insular Cortex, BA13	HIGH & LOW Specific	-0.082	-0.123	BL>FU	1.742	550	0.082*	0.074
				HIGH Specific	-0.123	-0.091	FU>BL	-1.086	288	0.278*	0.063
				LOW Specific	-0.037	-0.159	BL>FU	3.383	261	0.001	0.205

Abbreviations
BA: Brodmann Area; **BL>FU:** Baseline activation greater than Follow-up activation; **FU>BL:** Follow-up activation greater than Baseline activation; **r:** Pearson's correlation coefficient, **(*)**: not statistically significant at a p=0.05 level; **df:** degrees of Freedom.
High Specific: Scorers in upper 25% of CAPE 3-Items Score, n=366; **Low Specific:** Scorers in lower 25% CAPE 3-Items Score, n=330.

APPENDIX XVII: MID Study, fROI Brain Analysis, Tables of Results

Appendix XVII: General Stratification

MID Study, fROI Brain Analysis, CAPE General Stratification

Time-Point	Contrast	Analysis	MNI coordinates			Anatomical Area	K	p(FEW-corr) Cluster Level	p(FEW-corr) Peak Level	T score	Z score
			X	Y	Z						
BL	Feedback LW-NW	Low>High	33	41	40	Right Frontal Lobe, Middle Frontal Gyrus, BA09	1	0.015*	0.037*	5.04	4.88
BL	Feedback LW-NW	Group Average Negative	33	44	31	Right Frontal Lobe, Middle Frontal Gyrus, BA09	1	0.015*	0.05*	4.98	4.82
BL	Feedback LW-NW	Group Average Negative	-36	47	31	Left Frontal Lobe, Middle Frontal Gyrus, BA09/10	66	<0.0001	<0.0001	7.25	6.8
BL	Feedback LW-NW	Group Average Negative	-12	-28	40	Left Limbic Cortex, Cingulate Gyrus, BA31	28	<0.0001	<0.0001	7.37	6.9
FU	Anticipation LW-NW	Group Average Positive	9	8	1	Right Caudate Head	1073	<0.0001	<0.0001	11.67	Inf.

Abbreviations

BL: Baseline; **FU:** Follow-up; **LW:** Large Win; **NW**: No Win; **High Group**: Scorers in upper 10% of CAPE Total Score, n=149; **Low Group:** Scorers in lower 10% CAPE Total Score, n=149; **High>Low:** showing increased activation in the High but not in the Low Group; **Low>High:** showing increased activation in the Low but not in the High Group; **Group Average Positive:** showing increased activation in both High and Low Groups; **Group Average Negative:** showing decreased activation in both High and Low Groups; **BA:** Brodmann Area; **K:** number of Voxels; **p(FWE-corr):** p value corrected for Family Wise Error (false positives); **(*):** did not survive Bonferoni correction for multiple testing at p=0.008.

Appendix XVII: Specific Stratification

MID Study, fROI Brain Analysis, CAPE Specific Stratification

Time-Point	Contrast	Analysis	MNI coordinates			Anatomical Area	K	p(FEW-corr) Cluster Level	p(FEW-corr) Peak Level	T score	Z score
			X	Y	Z						
BL	Feedback LW-NW	Group Average Positive	57	-46	-14	Right Temp. Lobe, Inferior Temp. Gyrus, BA20/37	145	<0.0001	<0.0001	9.62	Inf.
BL	Feedback LW-NW	Group Average Positive	-30	-64	-32	Left Cerebellum, Uvula	11	<0.0001	<0.0001	5.79	5.68
FU	Anticipation LW-NW	Group Average Positive	-24	68	-8	Left Frontal Lobe, Superior Frontal Gyrus, BA10	2	0.006	0.005	5.39	5.27

Abbreviations

BL: Baseline; **FU:** Follow-up; **LW:** Large Win; **NW**: No Win; **High Group**: Scorers in upper 25% of CAPE 3-Items Score, n=366; **Low Group:** Scorers in lower 25% CAPE 3-Items Score, n=330; **High>Low:** showing increased activation in the High but not in the Low Group; **Low>High:** showing increased activation in the Low but not in the High Group; **Group Average Positive:** showing increased activation in both High and Low Groups; **Group Average Negative:** showing decreased activation in both High and Low Groups; **BA:** Brodmann Area; **K:** number of Voxels; **p(FWE-corr):** p value corrected for Family Wise Error (false positives).

APPENDIX XVIII: MID Study, Exploratory Cross-Sectional fROI Analysis, Tables of Results

Appendix XVIII: General Stratification

MID Study, Exploratory Cross-Sectional Analysis, Independent T-tests, CAPE General Stratification

Time-Point	MNI Coordinates			Anatomical Area	High Group Mean Brain Activation (Parameter Estimates)	Low Group Mean Brain Activation (Parameter Estimates)	Group Activation Relation	t-test for Equality of Means			
	X	Y	Z					t-test	df	Sig.	r
BL	33	41	40	Right Frontal Lobe, Middle Frontal Gyrus, BA09	-0.986	0.134	L>H	-5.069	188	<0.0001	0.346
BL	33	44	31	Right Frontal Lobe, Middle Frontal Gyrus, BA09	-1.011	-0.249	L>H	-3.029	188	0.003	0.215
BL	-36	47	31	Left Frontal Lobe, Middle Frontal Gyrus, BA09/10	-1.446	-0.637	L>H	-2.818	187	0.005	0.202
BL	-12	-28	40	Left Limbic Cortex, Cingulate Gyrus, BA31	-0.966	-0.426	L>H	-2.82	169	0.005	0.212
FU	9	8	1	Right Caudate Head	0.578	0.959	L>H	-2.846	141	0.005	0.233

Abbreviations

BL: Baseline; **FU:** Follow-up; **BA:** Brodmann Area; **H>L:** High Group showing more activation than Low Group; **L>H:** Low Group showing more activation than High Group; **r:** Pearson's correlation coefficient; **df:** degrees of Freedom.

Appendix XVIII: Specific Stratification

MID Study, Exploratory Cross-Sectional Analysis, Independent T-tests, CAPE Specific Stratification

Time-Point	MNI Coordinates			Anatomical Area	High Group Mean Brain Activation (Parameter Estimates)	Low Group Mean Brain Activation (Parameter Estimates)	Group Activation Relation	t-test for Equality of Means			
	X	Y	Z					t-test	df	Sig.	r
BL	57	-46	-14	Right Temporal Lobe, Inferior Temporal Gyrus, BA20/37	0.468	0.917	L>H	-3.126	445	0.002	0.147
BL	-30	-64	-32	Left Cerebellum, Uvula	0.214	0.686	L>H	-3.048	433	0.002	0.149
FU	-24	68	-8	Left Frontal Lobe, Superior Frontal Gyrus, BA10	0.107	0.257	L>H	-2.211	312	0.028	0.124

Abbreviations

BL: Baseline; **FU:** Follow-up; **BA:** Brodmann Area; **H>L:** High Group showing more activation than Low Group; **L>H:** Low Group showing more activation than High Group; **r:** Pearson's correlation coefficient; **df:** degrees of Freedom.

APPENDIX XIX: MID Study, Exploratory Longitudinal fROI Analysis, Tables of Results

Appendix XIX: General Stratification

MID Study, Exploratory Longitudinal Analysis, Paired T-tests, CAPE General Stratification

MNI Coordinates			Anatomical Area	Groups	Baseline Mean Brain Activation (Parameter Estimates)	Follow-up Mean Brain Activation (Parameter Estimates)	Group Activation Relation	t-test for Equality of Means			
X	Y	Z						t-test	df	Sig.	r
-36	47	31	Left Frontal Lobe, Middle Frontal Gyrus, BA09/10	HIGH & LOW General	-1.025	-0.482	FU>BL	-2.135	94	0.035	0.215
				HIGH General	-1.454	-0.397	FU>BL	-2.851	41	0.007	0.407
				LOW General	-0.684	-0.548	FU>BL	-0.399	52	0.692*	0.055
33	44	31	Right Frontal Lobe, Middle Frontal Gyrus, BA09	HIGH & LOW General	-0.711	-0.223	FU>BL	-2.094	94	0.039	0.212
				HIGH General	-1.055	-0.230	FU>BL	-2.902	41	0.006	0.413
				LOW General	-0.437	-0.218	FU>BL	-0.629	52	0.532*	0.087
33	41	40	Right Frontal Lobe, Middle Frontal Gyrus, BA09	HIGH & LOW General	-0.461	-0.248	FU>BL	-0.896	94	0.373*	0.092
				HIGH General	-1.046	-0.131	FU>BL	-3.18	41	0.003	0.445
				LOW General	0.002	-0.342	BL>FU	1.009	52	0.318*	0.138

Abbreviations

BA: Brodmann Area; **BL>FU:** Baseline activation greater than Follow-up activation; **FU>BL:** Follow-up activation greater than Baseline activation; **r:** Pearson's correlation coefficient: **(*)**: not statistically significant at a p=0.05 level; **df:** degrees of Freedom.

High General: Scorers in upper 10% of CAPE Total Score, n=149; **Low General:** Scorers in lower 10% CAPE Total Score, n=149.

Appendix XIX: Specific Stratification

MID Study, Exploratory Longitudinal Analysis, Paired T-tests, CAPE Specific Stratification

MNI Coordinates			Anatomical Area	Groups	Baseline Mean Brain Activation (Parameter Estimates)	Follow-up Mean Brain Activation (Parameter Estimates)	Group Activation Relation	t-test for Equality of Means			
X	Y	Z						t-test	df	Sig.	r
-30	-64	-32	Left Cerebellum, Uvula	HIGH & LOW Specific	0.291	0.156	BL>FU	0.902	219	0.368*	0.061
				HIGH Specific	0.072	0.238	FU>BL	-0.827	118	0.41*	0.076
				LOW Specific	0.549	0.059	BL>FU	2.249	100	0.027	0.219

Abbreviations

BA: Brodmann Area; **BL>FU:** Baseline activation greater than Follow-up activation; **FU>BL:** Follow-up activation greater than Baseline activation; **r:** Pearson's correlation coefficient: **(*)**: not statistically significant at a p=0.05 level; **df:** degrees of Freedom.

High Specific: Scorers in upper 25% of CAPE 3-Items Score, n=366; **Low Specific:** Scorers in lower 25% CAPE 3-Items Score, n=330.

APPENDIX XX: CANTAB Exploratory Cross-Sectional & Longitudinal Analysis, Tables of Results

Appendix XX: Cross-Sectional Analysis

CANTAB Measures Exploratory Cross-Sectional Analysis, Independent T-tests, CAPE General and Specific Stratification

CANTAB Variable	Stratification	Timepoint	High Group Mean Score	Low Group Mean Score	Group Scores Relation	t-test for Equality of Means			
						t-test	df	Sig.	r
AGN Total Omissions Negative	General	BL	10.052	13.177	L>H	-3.021	235	0.003	0.193
AGN Total Omissions Positive	General	BL	12.035	14.645	L>H	-2.817	237	0.005	0.180
CGT Risk Adjustment	Specific	BL	1.453	1.706	L>H	-3.043	576	0.002	0.126

Abbreviations

AGN Total Omissions Negative/Positive: Affective Go-NoGo Task, total number of missed responses to targets in the blocks specified by the value of target type (negative, positive); **CGT Risk Adjustment:** Cambridge Gambling Task, tendency to get higher proportions of points when the large majority of boxed are the colour chosen; **General Stratification:** using CAPE Total Score (*High Group:* Scorers in upper 10% of CAPE Total Score, n=149; *Low Group:* Scorers in lower 10% CAPE Total Score, n=149); **Specific Stratification:** using CAPE 3-Items Score (*High Group:* Scorers in upper 25% of CAPE 3-Items Score, n=366*; Low Group:* Scorers in lower 25% CAPE 3-Items Score, n=330); **H>L:** High Group showing greater scores than Low Group; **L>H:** Low Group showing greater scores than High Group; **r:** Pearson's correlation coefficient; **BL:** Baseline; **FU:** Follow-up; **df:** degrees of Freedom

Appendix XX: Longitudinal Analysis

CANTAB Measures Exploratory Longitudinal Analysis, Paired T-tests, CAPE General and Specific Stratification

CANTAB Variable	Group	Baseline Mean Score	Follow-up Mean Score	Group Scores Relation	t-test for Equality of Means			
					t-test	df	Sig.	r
AGN Total Omissions Negative	ALL	11.899	6.647	BL>FU	18.932	781	<0.0001	0.561
	HIGH General	10.065	6.688	BL>FU	3.745	76	<0.0001	0.395
	LOW General	12.369	7.095	BL>FU	6.385	83	<0.0001	0.574
AGN Total Omissions Positive	ALL	13.787	8.551	BL>FU	19.853	781	<0.0001	0.579
	HIGH General	12.195	8.273	BL>FU	4.529	76	<0.0001	0.461
	LOW General	14.274	8.964	BL>FU	6.352	83	<0.0001	0.572
CGT Risk Adjustment	ALL	1.606	1.934	FU>BL	-11.329	1131	<0.0001	0.319
	HIGH Specific	1.447	1.883	FU>BL	-7.313	282	<0.0001	0.399
	LOW Specific	1.702	1.891	FU>BL	-3.058	260	<0.0001	0.186

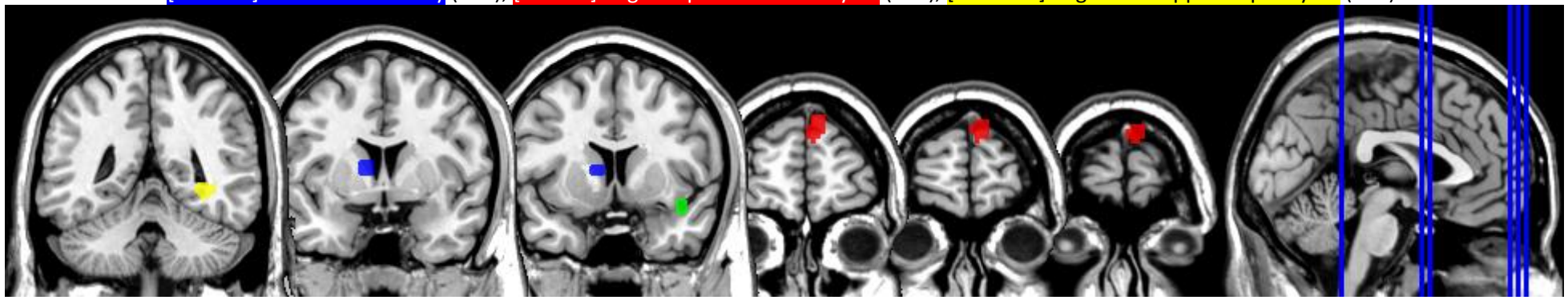
Abbreviations

AGN Total Omissions Negative/Positive: Affective Go-NoGo Task, total number of missed responses to targets in the blocks specified by the value of target type (negative, positive); **CGT Risk Adjustment:** Cambridge Gambling Task, tendency to get higher proportions of points when the large majority of boxed are the colour chosen; **BL>FU:** Mean Scores greater at BL; **FU>BL:** Mean Scores greater at FU; **r:** Pearson's correlation coefficient; **BL:** Baseline; **FU:** Follow-up: **ALL:** Whole sample, n=1,434: **High General**: Scorers in upper 10% of CAPE Total Score, n=149; **Low General:** Scorers in lower 10% CAPE Total Score, n=149: **High Specific**: Scorers in upper 25% of CAPE 3-Items Score, n=366; **Low Specific:** Scorers in lower 25% CAPE 3-Items Score, n=330; **df:** degrees of Freedom

APPENDIX XXI: FT Study, fROIs Illustrations, CAPE General Stratification

FT Study, CAPE General Stratification, ROIs selected for analysis, Coronal View

BASELINE	[42 8 -14]: Right Insular Cortex (H>L)
FOLLOW-UP	[-12 5 10]: Left Caudate Body (L>H); [6 65 31]: Right Superior Frontal Gyrus (L>H); [33 -46 -5]: Right Parahippocampal Gyrus (L>H)



Horizontal Axis: Left=Left, Right=Right

Vertical Axis: Up=Superior, Down=Inferior

FT Study, CAPE General Stratification, ROIs selected for analysis, Sagittal View

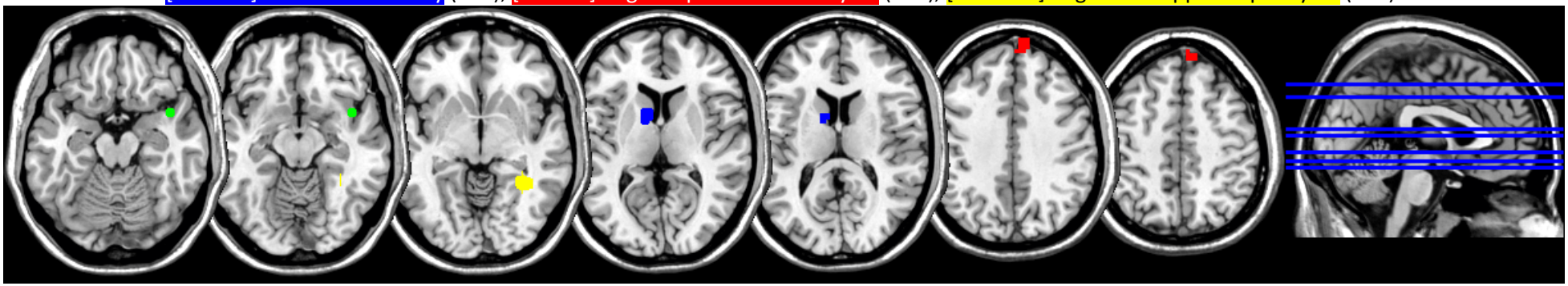
BASELINE	[42 8 -14]: Right Insular Cortex (H>L)
FOLLOW-UP	[-12 5 10]: Left Caudate Body (L>H); [6 65 31]: Right Superior Frontal Gyrus (L>H); [33 -46 -5]: Right Parahippocampal Gyrus (L>H)

Horizontal Axis: Left=Posterior, Right=Anterior

Vertical Axis: Up=Superior, Down=Inferior

FT Study, CAPE General Stratification, ROIs selected for analysis, Axial View

BASELINE	[42 8 -14]: Right Insular Cortex (H>L)
FOLLOW-UP	[-12 5 10]: Left Caudate Body (L>H); [6 65 31]: Right Superior Frontal Gyrus (L>H); [33 -46 -5]: Right Parahippocampal Gyrus (L>H)



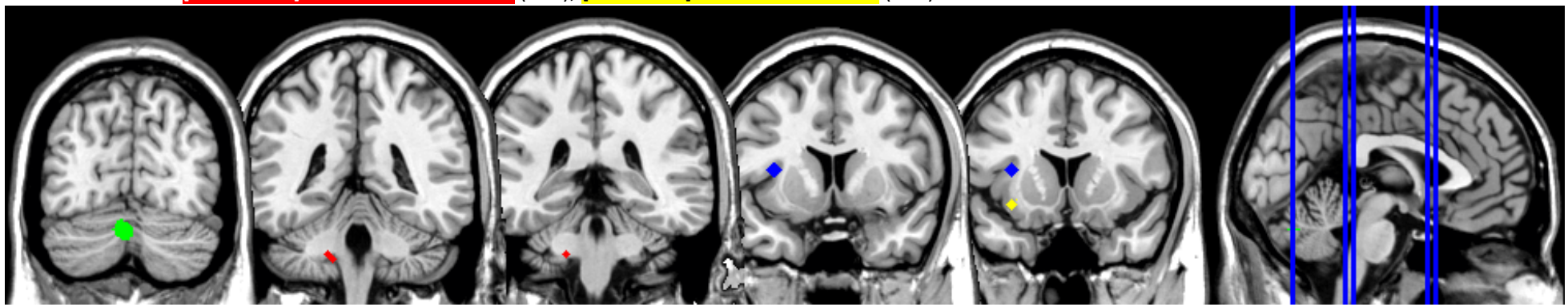
Horizontal Axis: Left=Left, Right=Right

Vertical Axis: Up=Anterior, Down=Posterior

APPENDIX XXII: FT Study, fROIs Illustrations, CAPE Specific Stratification

FT Study, CAPE Specific Stratification, ROIs selected for analysis, Coronal View

BASELINE	[-6 -73 -26]: Left Cerebellar Declive (H>L); [-33 11 10]: Left Insular Cortex (L>H)
FOLLOW-UP	[-15 -40 -44]: Left Cerebellar Tonsil (L>H); [-33 17 -11]: Left Insular Cortex (L>H)

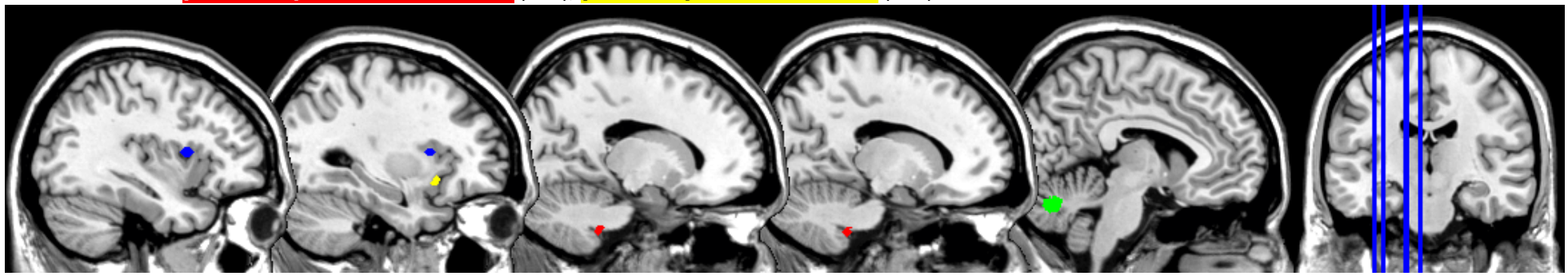


Horizontal Axis: Left=Left, Right=Right

Vertical Axis: Up=Superior, Down=Inferior

FT Study, CAPE Specific Stratification, ROIs selected for analysis, Sagittal View

BASELINE	[-6 -73 -26]: Left Cerebellar Declive (H>L); [-33 11 10]: Left Insular Cortex (L>H)
FOLLOW-UP	[-15 -40 -44]: Left Cerebellar Tonsil (L>H); [-33 17 -11]: Left Insular Cortex (L>H)

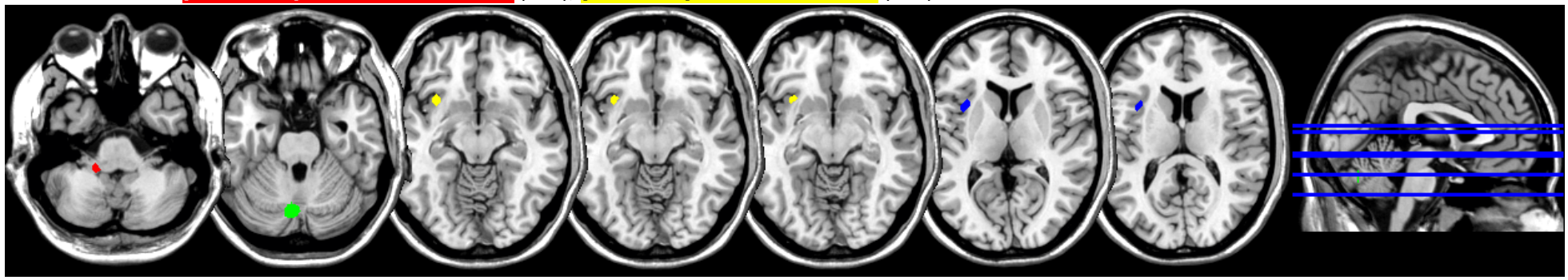


Horizontal Axis: Left=Posterior, Right=Anterior

Vertical Axis: Up=Superior, Down=Inferior

FT Study, CAPE Specific Stratification, ROIs selected for analysis, Axial View

BASELINE	[-6 -73 -26]: Left Cerebellar Declive (H>L); [-33 11 10]: Left Insular Cortex (L>H)
FOLLOW-UP	[-15 -40 -44]: Left Cerebellar Tonsil (L>H); [-33 17 -11]: Left Insular Cortex (L>H)



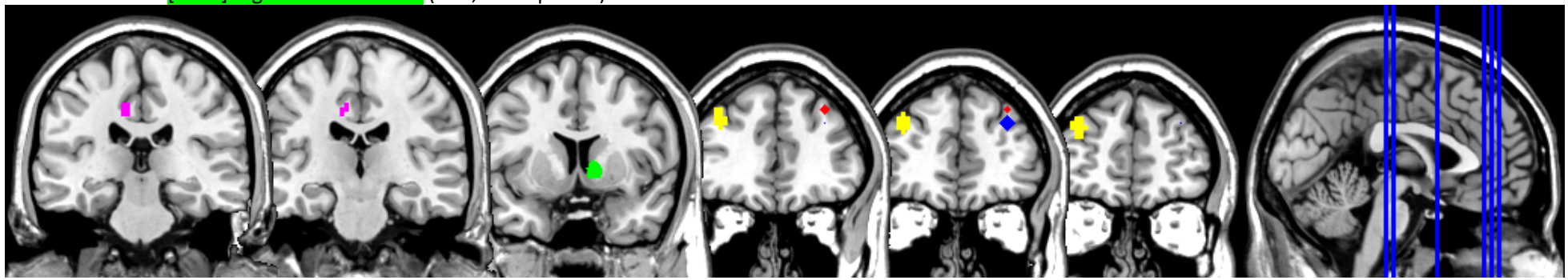
Horizontal Axis: Left=Left, Right=Right

Vertical Axis: Up=Anterior, Down=Posterior

APPENDIX XXIII: MID Study, fROIs Illustrations, CAPE General Stratification

MID Study, CAPE General Stratification, ROIs selected for analysis, Coronal View

BASELINE	[33 41 40] Right Middle Frontal Gyrus (L>H, Feedback); [33 44 31] Right Middle Frontal Gyrus (L>H, Feedback); [-36 47 31] Left Middle Frontal Gyrus (L>H, Feedback); [-12 -28 40] Left Cingulate Gyrus (L>H, Feedback)
FOLLOW-UP	[9 8 1] Right Caudate Head (L>H, Anticipation)

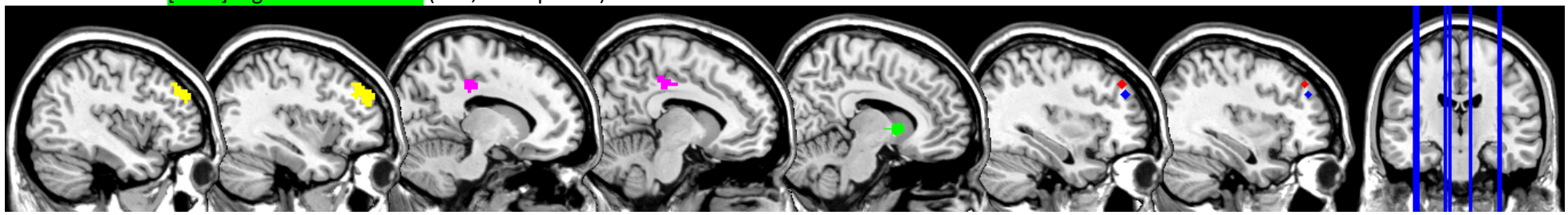


Horizontal Axis: Left=Left, Right=Right

Vertical Axis: Up=Superior, Down=Inferior

MID Study, CAPE General Stratification, ROIs selected for analysis, Sagittal View

BASELINE	[33 41 40] Right Middle Frontal Gyrus (L>H, Feedback); [33 44 31] Right Middle Frontal Gyrus (L>H, Feedback); [-36 47 31] Left Middle Frontal Gyrus (L>H, Feedback); [-12 -28 40] Left Cingulate Gyrus (L>H, Feedback)
FOLLOW-UP	[9 8 1] Right Caudate Head (L>H, Anticipation)

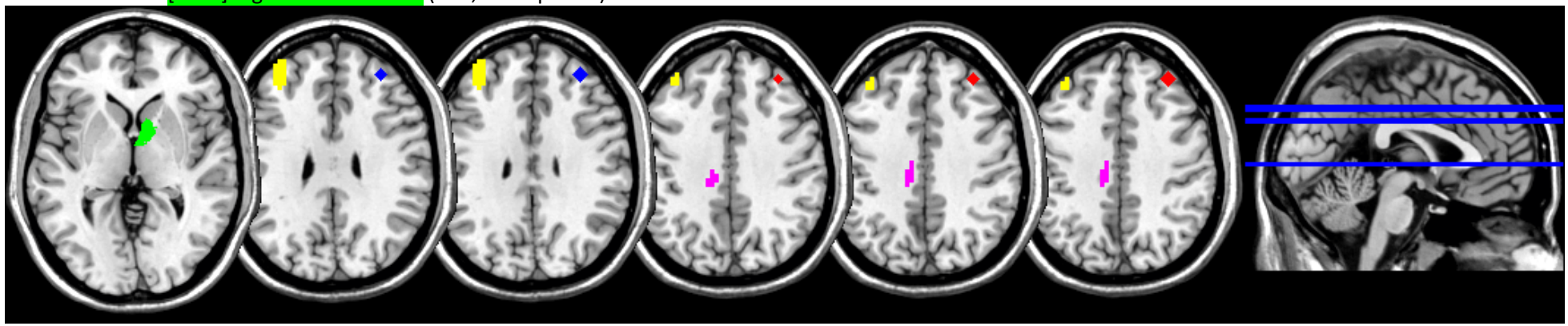


Horizontal Axis: Left=Posterior, Right=Anterior

Vertical Axis: Up=Superior, Down=Inferior

MID Study, CAPE General Stratification, ROIs selected for analysis, Axial View

BASELINE	[33 41 40] Right Middle Frontal Gyrus (L>H, Feedback); [33 44 31] Right Middle Frontal Gyrus (L>H, Feedback); [-36 47 31] Left Middle Frontal Gyrus (L>H, Feedback); [-12 -28 40] Left Cingulate Gyrus (L>H, Feedback)
FOLLOW-UP	[9 8 1] Right Caudate Head (L>H, Anticipation)



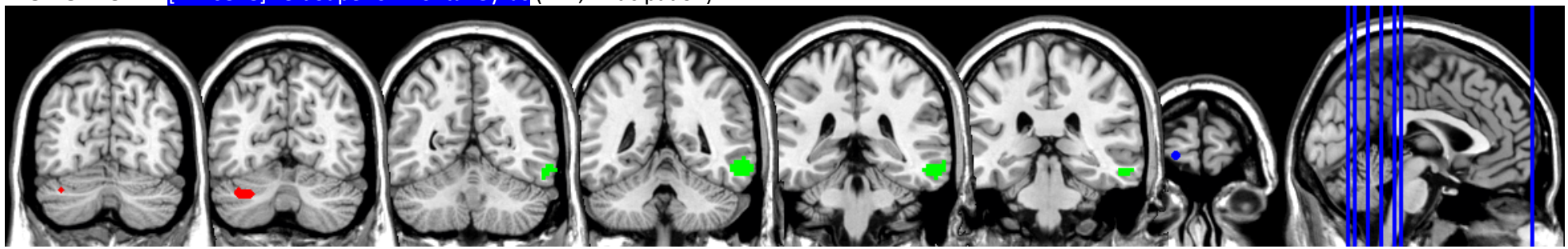
Horizontal Axis: Left=Left, Right=Right

Vertical Axis: Up=Anterior, Down=Posterior

APPENDIX XXIV: MID Study, fROIs Illustrations, CAPE Specific Stratification

MID Study, CAPE Specific Stratification, ROIs selected for analysis, Coronal View

BASELINE	[57 -46 -14] Right Inferior Temporal Gyrus (L>H, Feedback); [-30 -64 -32] Left Cerebellar Uvula (L>H, Feedback)
FOLLOW-UP	[-24 68 -8] Left Superior Frontal Gyrus (L>H, Anticipation)

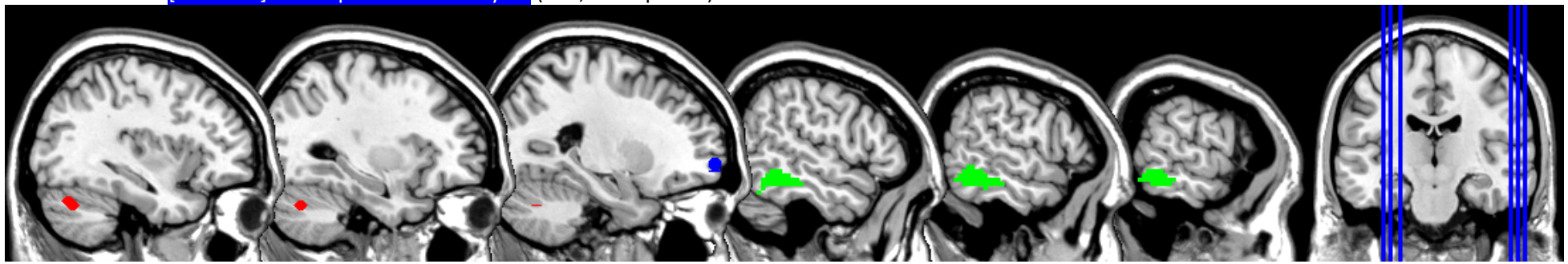


Horizontal Axis: Left=Left, Right=Right

Vertical Axis: Up=Superior, Down=Inferior

MID Study, CAPE Specific Stratification, ROIs selected for analysis, Sagittal View

BASELINE	[57 -46 -14] Right Inferior Temporal Gyrus (L>H, Feedback); [-30 -64 -32] Left Cerebellar Uvula (L>H, Feedback)
FOLLOW-UP	[-24 68 -8] Left Superior Frontal Gyrus (L>H, Anticipation)

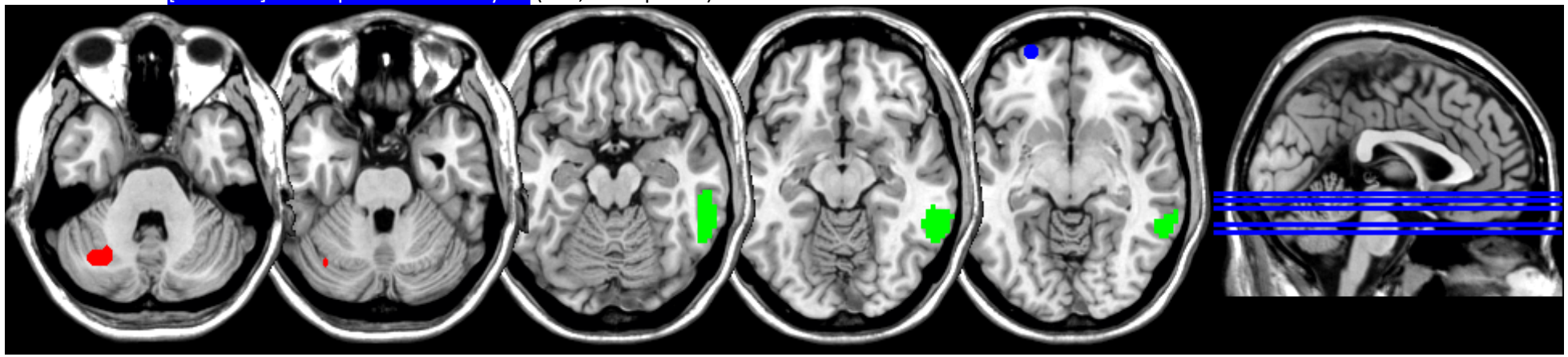


Horizontal Axis: Left=Posterior, Right=Anterior

Vertical Axis: Up=Superior, Down=Inferior

MID Study, CAPE Specific Stratification, ROIs selected for analysis, Axial View

BASELINE	[57 -46 -14] Right Inferior Temporal Gyrus (L>H, Feedback); [-30 -64 -32] Left Cerebellar Uvula (L>H, Feedback)
FOLLOW-UP	[-24 68 -8] Left Superior Frontal Gyrus (L>H, Anticipation)



Horizontal Axis: Left=Left, Right=Right

Vertical Axis: Up=Anterior, Down=Posterior

APPENDIX XXV: Correlations between fROIs BOLD signals, and selected CANTAB and CAPE scores

Baseline Correlations between BOLD signals, and selected CANTAB and CAPE scores

	Task, Stratification	fROI	CAPE Grand Total, FU	CAPE Positive Symptoms Total, FU	CAPE Negative Symptoms Total, FU	CAPE 3-Items Total, FU	CANTAB AGN Total Omissions Negative, BL	CANTAB AGN Total Omissions Positive, BL
Mean Parameter Estimates, BL	FT, General	[42 8 -14]	**0.292** (p<0.0001)	**0.308** (p<0.0001)	**0.264** (p<0.0001)	**0.265** (p<0.0001)	**-0.181** (p=0.011)	**-0.219** (p=0.002)
	FT, Specific	[-6 -73 -26]	**0.096** (p=0.024)	**0.105** (p=0.014)		**0.125** (p=0.03)		
		[-33 11 10]	**-0.128** (p=0.003)	**-0.108** (p=0.011)	**-0.139** (p=0.001)	**-0.127** (p=0.003)		
	MID, Feedback, General	[33 41 40]	**-0.373** (p<0.0001)	**-0.293** (p=0.004)	**-0.367** (p<0.0001)	**-0.296** (p=0.004)		
	MID, Feedback, Specific	[57 -46 -14]		**-0.142** (p=0.036)				
		[-30 -64 -32]	**-0.173** (p=0.01)	**-0.204** (p=0.002)	**-0.190** (p=0.005)	**-0.195** (p=0.004)		
	MID, Anticipation, Specific	[-24 68 -8]	**-0.150** (p=0.006)	**-0.114** (p=0.038)	**-0.160** (p=0.03)			

In bold: Spearman's rho (correlation coefficient), non-parametric; p: 2-tailed significance level; only statistically significant correlations are displayed.

Follow-up Correlations between BOLD signals, and selected CANTAB and CAPE scores

	Task, Stratification	fROI	CAPE Grand Total, FU	CAPE Positive Symptoms Total, FU	CAPE Negative Symptoms Total, FU	CAPE 3-Items Total, FU	CANTAB AGN Total Omissions Negative, FU
Mean Parameter Estimates, FU	FT, General	[42 8 -14]					**0.163** (p=0.030)
		[6 65 31]	**-0.173** (p=0.008)	**-0.179** (p=0.006)	**-0.130** (p=0.048)	**-0.142** (p=0.03)	
		[33 -46 -5]	**-0.133** (p=0.042)	**-0.177** (p=0.07)	**-0.164** (p=0.012)	**-0.144** (p=0.29)	
	FT, Specific	[-33 17 -11]	**-0.113** (p=0.008)	**-0.121** (p=0.004)		**-0.110** (p=0.009)	
	MID, Feedback, General	[-12 -28 40]		**-0.169** (p=0.043)		**-0.180** (p=0.032)	
	MID, Anticipation, General	[9 8 1]	**-0.235** (p=0.005)	**-0.222** (p=0.008)	**-0.257** (p=0.002)	**-0.218** (p=0.009)	
	MID, Feedback, Specific	[57 -46 -14]			**-0.117** (p=0.033)		
	MID, Anticipation, Specific	[-24 68 -8]	**-0.150** (p=0.006)				

In bold: Spearman's rho (correlation coefficient), non-parametric; p: 2-tailed significance level; only statistically significant correlations are displayed.

APPENDIX XXVI: Publication

Papanastasiou E, Mouchlianitis E, Joyce DW, et al. **Examination of the Neural Basis of Psychoticlike Experiences in Adolescence During Reward Processing.** *JAMA Psychiatry.* Published online August 01, 2018. doi:10.1001/jamapsychiatry.2018.1973 [254]

Research

JAMA Psychiatry | Original Investigation

Examination of the Neural Basis of Psychoticlike Experiences in Adolescence During Reward Processing

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IMPORTANCE Psychoticlike experiences (PLEs) are subclinical manifestations of psychotic symptoms and may reflect an increased vulnerability to psychotic disorders. Contemporary models of psychosis propose that dysfunctional reward processing is involved in the cause of these clinical illnesses.

OBJECTIVE To examine the neuroimaging profile of healthy adolescents at 14 and 19 years old points with PLEs, using a reward task.

DESIGN, SETTING, AND PARTICIPANTS A community-based cohort study, using both a cross-sectional and longitudinal design, was conducted in academic centers in London, Nottingham, United Kingdom, and Dublin, Ireland; Paris, France; and Berlin, Hamburg, Mannheim, and Dresden, Germany. A group of 1434 healthy adolescent volunteers was evaluated, and 2 subgroups were assessed at ages 14 and 19 years. Those who scored as either high or low PLE (based on the upper and lower deciles) on the Community Assessment of Psychic Experiences Questionnaire (CAPE-42) at age 19 years were included in the analysis. The study was conducted from January 1, 2016, to January 1, 2017.

MAIN OUTCOMES AND MEASURES Participants were assessed at age 14 and 19 year points using functional magnetic resonance imaging while performing a monetary incentive delay reward task. A first-level model focused on 2 predefined contrasts of anticipation and feedback of a win. The second-level analysis examined activation within the reward network using an a priori–defined region of interest approach. The main effects of group, time, and their interaction on brain activation were examined.

RESULTS Of the 1434 adolescents, 2 groups (n = 149 each) (high PLEs, n = 149, 50 [33.6%] male; low PLEs, n = 149, 84 [56.4%] male) were compared at ages 14 and 19 years. Two regions within the left and right middle frontal gyri showed a main effect of time on brain activation ($F_{1, 93}$ = 5.559; P = .02; $F_{1, 93}$ = 5.009; P = .03, respectively); there was no main effect of group. One region within the right middle frontal gyrus demonstrated a significant time × group interaction ($F_{1, 93}$ = 7.448; P = .01).

CONCLUSION AND RELEVANCE The findings are consistent with evidence implicating alterations in prefrontal and striatal function during reward processing in the etiology of psychosis. Given the nature of this nonclinical sample this may reflect a combination of aberrant salience yielding abnormal experiences and a compensatory cognitive control mechanism necessary to contextualize them.

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Supplemental content

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Research Original Investigation Examination of the Neural Basis of Psychoticlike Experiences in Adolescence During Reward Processing

Psychoticlike experiences (PLEs) describe transitory symptoms that, if they persist, lead to clinically relevant symptoms with functional impairment.[1] This contemporary view proposes that psychotic symptoms are not "all-or-nothing" pathologic phenomena, but rather fall within the spectrum of normal experiences, conceptualized as the continuum model of psychosis.[2] This view is supported by the high prevalence rate of delusional or hallucinatory experiences in the general population (10% and 30%), which is substantially higher than the prevalence rates of psychotic disorders.[3] Late adolescence is a critical neurodevelopmental period in psychosis, with the classic age at onset being in early adulthood. Approximately 20% to 35% of individuals aged 12 to 35 years who meet clinical criteria for a prodromal risk syndrome (ie, the Comprehensive Assessment of the At-Risk Mental State structured questionnaire administered by clinicians) convert to psychosis within 2 years.[4] The presence of psychotic symptoms at age 11 years and cannabis use by the age of 15 years were the 2 strongest predictors of psychosis outcomes at age 26 years.[5] The most widely used community assessment of PLEs is the Community Assessment of Psychic Experiences Questionnaire (CAPE).[6]

Psychoticlike experiences offer a useful, nonclinical phenotype to study psychotic disorders[7] with the advantages of a lack of exposure to the illness and antipsychotic medication, a critical phase of neurodevelopment for psychosis in drug-naive individuals. The aberrant salience model of psychosis suggests that positive psychotic symptoms occur when dysregulated dopamine firing in the mesocorticolimbic system gives rise to attribution of significance to irrelevant perceptual stimuli.[8] Patients with first-episode psychosis exhibit abnormal physiologic responses associated with reward prediction error in the dopaminergic midbrain, striatum, and limbic system and subtle abnormalities in discriminating between motivationally salient and more neutral stimuli.[9]

A small functional magnetic resonance imaging (fMRI) study of individuals with PLEs (n = 27) at age 14 years using a reward task demonstrated increased amygdala/hippocampal activation in face perception tasks and reduced right dorsolateral prefrontal activation in response inhibition tasks.[10] An earlier study suggested that PLEs arise as a consequence of decreased cognitive control,[11] a view that is supported by a more recent systematic review of schizophrenia.[12] In summary, the presence of psychosis symptoms is associated with decreases in striatal activation during reward tasks and a reduction in prefrontal activation in areas implicated in cognitive control. However, the frequency and intensity of psychotic symptoms differ from those in the general population sample through ultra-high-risk (UHR) states to schizophrenia and the latter is further differentiated by the presence of functional deterioration.[13] If the cognitive control hypothesis is correct, one might anticipate dysregulation in subcortical reward processing in healthy adolescents that is compensated for by intact cognitive control mechanisms.

A combination of the aberrant salience and cognitive control hypotheses suggests that the presence of aberrant salience may generate PLEs, but these experiences are contextualized appropriately (ie, with no significant functional consequences) if cognitive control mechanisms are operating efficiently. Failure of cognitive control mechanisms would manifest as clinically relevant symptoms with consequent functional deterioration evidenced as psychotic illness.

The aim of the study was to determine whether PLEs in adolescence are associated with altered prefrontal and striatal activation during reward processing. We used the IMAGEN database[14] sample of 1434 healthy adolescents to examine the association between elevated CAPE-42 scores and striatal and prefrontal activation associated with salience and cognitive control, respectively. Two hypotheses were evaluated: the presence of high PLEs will be associated with decreased activation of the prefrontal cortex and striatum during reward processing[15,16] and the pattern of activation in the prefrontal cortex and striatum will vary between high and low PLE groups over time between early and late adolescence, consistently with reports in the literature on patients with psychosis.

Key Points

Question Are psychoticlike experiences in adolescents associated with altered prefrontal and striatal activation during reward processing?

Findings In this cohort study of 298 adolescents, those with an elevated rate of psychoticlike experiences at age 14 years demonstrated reduced activation in prefrontal and limbic cortical areas during reward processing compared with adolescents with no psychoticlike experiences. However, by age 19 years, the group with the elevated rate of psychoticlike experiences showed differentially increased activation of the right prefrontal cortex and reduced activation of dorsal striatum.

Meaning Adolescents with an elevated rate of psychoticlike experiences show differential activation in frontostriatal brain areas engaged during reward processing compared with control adolescents; given the nonclinical nature of the sample, the increase in prefrontal cortical activation from early to late adolescence may reflect a compensatory cognitive mechanism in the presence of abnormal striatal reward processing to contextualize these abnormal experiences.

Methods

Participants and Settings

Neuroimaging and clinical data of healthy adolescents were obtained from the IMAGEN database.[14] The IMAGEN study received ethical approval by the ethics research committees of the academic centers at which the study was conducted (London, Nottingham, UK, and Dublin, Ireland; Paris, France; and Berlin, Hamburg, Mannheim, and Dresden, Germany). All adult participants provided written consent; minors provided oral consent and written consent was obtained by their parents or legal guardians. The present study was conducted from January 1, 2016, to January 1, 2017, from deidentified data. Access to IMAGEN database for the conduction of the present study did not require a separate informed consent; a waiver was applied owing to anonymized data. We used data from age 14 and 19 year points. A total of 1434 adolescents was initially selected based on quality controls and completeness of their behavioral and neuroimaging data sets. Two subgroups were

assessed at ages 14 and 19 years. Those who scored as either high or low PLE (based on the upper and lower deciles) on the CAPE 42 items instrument (CAPE-42) at age 19 years were included in the analysis. The epidemiologic features of our sample are described in **Table 1**.

Measures

The CAPE-42 questionnaire[6] was used as a measure of PLEs in our adolescent population at age 19 years. In its extended version CAPE-42 includes 42 items that are grouped in 3 dimensions: positive, negative, and depressive. Each item is scored for frequency and severity in a scale from 0 to 7; total scores range from 0 to 294. Higher scores indicate an elevated presence of prodromal psychotic symptoms.

The Cambridge Neuropsychological Test Automated Battery (CANTAB) includes highly sensitive, precise, and objective measures of cognitive function.[17] Our study focused on the Affective Go-NoGo Task (AGN), providing an assessment of the information processing biases for positive and negative stimuli; this task was chosen as a proxy for "hot" cognition, as related to the inhibitory/affective function of frontal and limbic areas of the brain.

The adapted monetary incentive delay (MID) task is a widely used assessment of rewarded learning. It measures participant reactions to a brief visual target. The MID task includes reward anticipation and receipt of feedback of win or no-win outcomes.

Stratification of the Sample

We defined 2 subgroups with high or low PLEs, based on total CAPE-42 scores. Because the CAPE-42 total scores did not follow a normal distribution, we selected participants with high and low scores using the upper and lower deciles. This distinction resulted in 149 adolescents in the high PLEs group and 149 in the low PLEs group. The high group CAPE-42 total score ranged from 91 to 182, corresponding to an itemized score range of 2.17 to 4.33. Cutoff levels in the area of 2.0 per CAPE-42 item provide adequate positive predictive value for transition to psychosis[18]; the level formed the lower bound of the high PLEs group. The 2 groups were matched for handedness, age, and IQ.

fMRI Acquisition and Analysis

The scanning parameters and sequence protocol were chosen to be uniform for all sites and scanners. A full description of the scanning protocols, cross-site standardization and quality checks, and preprocessing of resulting data are provided elsewhere.[19]

First-Level Analysis

Two within-participant contrasts reflecting core reward processing, as previously described,[20,21] were selected for investigation. The fMRIs were conducted at ages 14 and 19 years, using SPM12 (http://www.fil.ion.ucl.ac.uk/spm; Wellcome Trust Centre for Neuroimaging): anticipation of large win - anticipation of no win and feedback of large win - feedback of no win.

Second-Level Analysis

Whole-brain analysis focused only on high and low CAPE-42 scorers and task-related regions of interest for the 2 first-level contrasts were collapsed across the high and low groups. This approach provides an unbiased estimate of the activation, as the group average positive/negative is orthogonal to high greater than low or low greater than high and is also supported by literature on functional localizers.[22]

In a factorial analysis, the main effect of time, group, and the interaction of time × group on brain activation levels was examined by employing a mixed-model 2-way analysis of variance, with group as fixed and subject as random effects. Any main effects or interactions were further examined by post hoc

Table 1. Participant Characteristics and CAPE-42 Score Stratification

	CAPE-42 Total Score Stratification					
	High (n = 149)[a]			Low (n = 149)[b]		
Characteristic	Mean	SE	SD	Mean	SE	SD
Male, No. (%)	50 (33.6)			84 (56.4)		
Right handed, No. (%)	128 (85.9)			123 (82.6)		
Age, y						
Baseline	14.47	0.03	0.39	14.43	0.03	0.38
Follow-up	19.02	0.06	0.76	18.98	0.06	0.74
WISC baseline score[c]						
Verbal	111.15	1.32	15.66	106.72	1.27	15.24
Performance	108.49	1.33	15.79	105.2	1.20	14.42
ADRS total score, follow-up[d]	15.89	0.24	2.96	19.7	0.06	0.72
AUDIT total score, follow-up[e]	7.5	0.44	5.34	5.26	0.32	3.87
DAST total score, follow-up[f]	1.59	0.21	2.52	0.54	0.08	1.02
CAPE-42 score, follow-up[g]						
Total	111.64	1.74	21.26	9.54	0.39	4.75
Positive symptoms	33.09	1.27	15.48	3.23	0.24	2.98
Bizarre delusions	13.17	0.97	11.82	0.37	0.09	1.09
Social delusions	19.91	0.54	6.57	2.87	0.21	2.61
Negative symptoms	46.37	0.93	11.37	2.22	0.21	2.61
Depressive symptoms	32.18	0.61	7.49	4.09	0.21	2.54

Abbreviations: ADRS, Adolescent Depression Rating Scale; AUDIT, Alcohol Use Disorders Identification Test; CAPE-42, Community Assessment of Psychic Experiences Questionnaire, 42 items instrument; DAST, Drug Abuse Screening Test for Cannabis; WISC, Wechsler Intelligence Scale for Children.

[a] Scorers in upper 10% of CAPE-42 total score.

[b] Scorers in lower 10% of CAPE-42 total score.

[c] The average score is 100; higher scores indicate higher than average intelligence and lower scores indicate lower levels of intelligence.[37]

[d] Scores range from 0 to 60; higher scores indicate higher levels of adolescent depression.[38]

[e] Scores range from 0 to 40; higher scores indicate greater levels of alcohol abuse.[39]

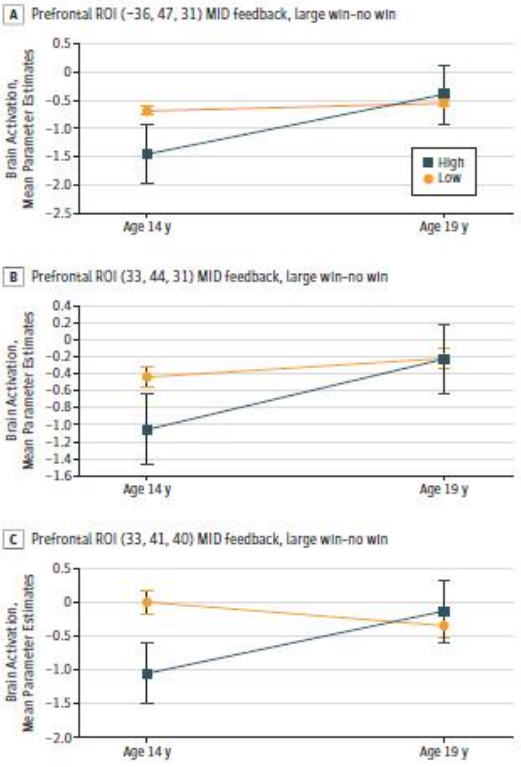
[f] Scores range from 0 to 10; higher scores indicate greater levels of cannabis abuse.[40]

[g] Scores range from 0 to 294; higher scores indicate elevated presence of prodromal psychotic symptoms.[6]

Figure 1. Regions of Interest Showing Differences in Brain Activation Between Low (L) and High (H) Psychoticlike Experiences Groups

Coronal (A), sagittal (B), and axial (C) views. At age 14 years: right middle frontal gyrus (33, 41, 40 [red]) (L>H [low group has shown greater brain activation than high group]); right middle frontal gyrus (33, 44, 31 [blue]) (L>H); left cingulate gyrus (−12, −28, 40 [purple]) (L>H); and left middle frontal gyrus (L>H) (−36, 47, 31 [yellow]). At age 19 years: (9, 8, 1 [green]) right caudate head (L>H).

Figure 2. Mean Brain Activation Parameter Estimates at Ages 14 and 19 Years for Functional Regions of Interest



Statistically significant changes at $P = .05$ level for the high psychoticlike experiences group only; SE bars are displayed. MID indicates monetary incentive delay.

paired, independent, 2-tailed t tests, with $P < .05$ as the statistically significant threshold. Additional exploratory analysis was also reported, when statistically significant.

Results

Two groups of adolescents (high PLEs, n = 149; 50 [33.6%] males and low PLEs, n = 149; 84 [56.4%) males]) were compared at ages 14 and 19 years. The 2 groups were matched for handedness, age, and IQ.

Results of fMRI Analysis

Five regions of interest (ROIs) based on previous studies of reward processing in psychosis and UHR for psychosis[15,16] and located in the prefrontal cortices, the limbic areas, and the striatum, were selected for factorial analysis. The ROIs (Montreal Neurological Institute space coordinates) were right caudate head (9, 8, 1), right middle frontal gyrus (33, 41, 40), right middle frontal gyrus (33, 44, 31), left middle frontal gyrus (−36, 47, 31), and left cingulate gyrus (−12, −28, 40) (**Figure 1** and eFigure 1, eFigure 2, and eFigure 3 in the Supplement provide a visual representation of the ROIs and eTable 1 in the Supplement reports the results of the functional regions of interest brain analysis).

Right Caudate Head (9, 8, 1)

No effects of group × time, group, or time were found. Additional exploratory analysis showed higher brain activation of the low PLEs group compared with the high PLEs group at age 19 years during anticipation ($t = -2.846$; $P = .01$) (eTable 2 and eTable 3 in the Supplement).

Right Middle Frontal Gyrus (33, 41, 40)

There was an interaction effect of group × time ($F_{1, 93} = 7.448$; $P = .01$), showing significant increase in the high PLEs group from ages 14 to 19 years ($t = -3.18$; $P = .003$) with no change in the low PLEs group. Additional exploratory analysis exhibited higher brain activation of the low PLEs group compared with the high PLEs group at age 14 years during feedback ($t = -5.069$; $P < .001$) (**Figure 2**, **Table 2**, and eTable 3 and eTable 4 in the Supplement).

Right Middle Frontal Gyrus (33, 44, 31)

There was a main effect of time ($F_{1, 93} = 5.009$; $P = .03$), driven by an increase in brain activation from ages 14 to 19 years, significant only for the high PLEs group ($t = -2.902$, $P = .01$).

Table 2. Mean Brain Activation Contrast Parameter Estimates Factorial Analysis

Characteristic	Type III Sum of Squares	*df*	Mean Square	*F* Value	*P* Value	*r* Value[a]
Frontal ROI (33, 41, 40) brain activation						
Time	7.632	1	7.632	1.527	.22[b]	0.127
Group	4.108	1	4.108	3.598	.06[b]	0.193
Time × group	37.236	1	37.236	7.448	.008	0.272
Error (time)	464.966	93	5.000	NA	NA	NA
Error (group)	106.187	93	1.142	NA	NA	NA
Frontal ROI (33, 44, 31) brain activation						
Time	25.604	1	25.604	5.009	.03	0.226
Group	2.323	1	2.323	1.821	.18[b]	0.139
Time × group	8.606	1	8.606	1.684	.20[b]	0.133
Error (time)	475.398	93	5.112	NA	NA	NA
Error (group)	118.659	93	1.276	NA	NA	NA
Frontal ROI (−36, 47, 31) brain activation						
Time	33.354	1	33.354	5.559	.02	0.237
Group	2.24	1	2.24	1.77	.19[b]	0.137
Time × group	19.871	1	19.871	3.312	.07[b]	0.185
Error (time)	558.029	93	6	NA	NA	NA
Error (group)	117.68	93	1.265	NA	NA	NA

Abbreviations: ROI, region of interest; NA, not applicable.
[a] Pearson correlation coefficient.
[b] Not statistically significant at a $P = .05$ level.

Table 3. CANTAB Measures Factorial Analysis[a]

CANTAB Variable[b]	Factors	Type III Sum of Squares	*df*, *dfR*	Mean Square	*F* Value	*P* Value	*r* Value[c]
AGN total omissions negative	Time	3006.213	1, 159	3006.213	50.236	<.001	0.490
	Group	73.817	1, 159	73.817	2.498	.12[d]	0.124
	Time × group	144.599	1, 159	144.599	2.416	.12[d]	0.122
AGN total omissions positive	Time	3423.720	1, 159	3423.720	58.778	<.001	0.520
	Group	77.094	1, 159	77.094	2.919	.09[d]	0.134
	Time × group	77.335	1, 159	77.335	1.328	.25[d]	0.091

Abbreviations: AGN, Affective Go-NoGo Task; CANTAB, Cambridge Neuropsychological Test Automated Battery; *dfR*, *df*(error).
[a] Mixed-model, 2-way analysis of variance factorial analysis.
[b] Total number of missed responses to targets in the blocks specified by the value of target type (negative, positive).
[c] Pearson correlation coefficient.
[d] Not statistically significant at a $P = .05$ level.

Additional exploratory analysis exhibited higher brain activation of the low PLEs group compared with the high PLEs group at age 14 years during feedback ($t = -3.029$; $P = .003$) (Figure 2, Table 2, and eTable 3 and eTable 4 in the Supplement).

Left Middle Frontal Gyrus (−36, 47, 31)

There was a main effect of time ($F_{1, 93} = 5.559$; $P = .02$) that was driven by an increase in brain activation from ages 14 to 19 years, but was significant only for the high PLEs group ($t = -2.851$; $P = .01$). Additional exploratory analysis exhibited higher brain activation of the low PLEs group compared with the high PLEs group at age 14 years during feedback ($t = -2.818$; $P = .01$) (Figure 2, Table 2, and eTable 3 and eTable 4 in the Supplement).

Left Cingulate Gyrus (−12, −28, 40)

No effects of group × time, group, or time were reported. Additional exploratory analysis exhibited higher brain activation of the low PLEs group compared with the high PLEs group at age 14 years during feedback ($t = -2.82$; $P = .01$) (eTable 2 and eTable 3 in the Supplement).

Results CANTAB Measures Analysis

There was a significant effect of time on AGN total omissions for both positive ($F_{1, 159} = 58.778$; $P < .001$) and negative ($F_{1, 159} = 50.236$; $P < .001$) stimuli; however, there was no significant main effect of group and no interaction (**Table 3**). Post hoc analyses demonstrated the AGN total omissions for both positive and negative stimuli showed a decrease from ages 14 to 19 years across the high PLEs group (AGN positive: $t = 4.529$; $P < .001$; AGN negative: $t = 3.745$; $P < .001$) and the low PLEs group (AGN positive: $t = 6.352$; $P < .001$; AGN negative: $t = 6.385$; $P < .001$). The high PLEs group scored lower on AGN total omissions for both positive and negative stimuli at age 14 years (Table 3 and eTable 5, eTable 6, and eFigure 4 in the Supplement).

Discussion

Adolescents with high levels of PLEs at age 19 years demonstrated a novel significant increase in right frontal activation during a reward processing task between the ages of 14 and 19

years. They also exhibited decreased activation of the head of caudate during reward processing at 19 years, which is in line with earlier findings.[23] Previous studies in early adolescent high-risk populations have found decreased frontal brain activation compared with controls[16]; this is in line with our findings of lower frontal activation in our high PLEs group at age 14 years.

The contemporary view suggests that abnormal perceptions, such as PLEs, may be a relatively common occurrence and, in most cases, they are appropriately contextualized—a function of cognitive control—and no functional alterations occur. The pattern of decreased striatal activation and increased prefrontal activation supports the suggestion that the evolution of clinically relevant psychotic symptoms requires not only a deficit in striatal reward processing, but also a putative failure of compensatory frontal executive processes.[24,25] Thus, this increase in right frontal activation in PLEs may serve as a proxy of executive function—a compensatory mechanism to ensure that any unusual experiences secondary to reward processing deficits do not become incorrectly represented given the current context. The lack of any neuropsychological performance differences in executive functioning between the low and high PLE adolescent groups also lends additional support to this view. However, other possibilities are that this pattern of change in processing reward engages prefrontal cortex and striatum in a different way to generate PLEs in these individuals or that the differences reflect the allocation of potential resources in a proactive, healthy way.

In a study using an MID task, anticipation of reward loss-avoidance elicited significant activation of the ventral striatum in both controls and active participants with UHR for psychosis, with a tendency for less activation in the UHR group.[15] Individuals with UHR have been shown to be more likely to attribute motivational salience to irrelevant stimulus features, and this bias (and ventral striatum responses) were correlated with delusionlike symptoms[26]; ventral striatum/pallidum connectivity to the midbrain is also altered in people with UHR for psychosis.[27] Functional MRI studies with UHR individuals have shown ventral striatum hypoactivation and frontal hyperactivation during reward anticipation.[15,28]

Early hypoactivation in frontal areas might represent a trait in the development of psychosis, as it is commonly reported across all phases of the psychosis continuum, from prodromal to schizophrenia. Hypofrontality[29] and functional dysconnectivity of frontostriatal circuitry[30] may represent a risk phenotype for psychosis. A meta-analysis of neurofunctional correlates of vulnerability to psychosis revealed hypoactivation of dorsolateral prefrontal cortex and ventrolateral prefrontal cortex as the most common finding in UHR and first-episode psychosis populations.[31] Even in healthy individuals, aberrant frontostriatal prediction error signals correlate with delusionlike beliefs.[32] Our longitudinal studies confirmed the involvement of 3 frontal areas, showing hypoactivation in the high PLEs group at age 14 years, which also manifested higher levels of activation at 19 years. This change might represent the outcome of a corrective mechanism, targeting brain areas with an activation deficit at an early phase.

The dopamine hypothesis of schizophrenia specified subcortical hyperdopaminergia combined with prefrontal hypodopaminergia as the cardinal features of the neuropathologic cause of schizophrenia; this hypothesis has been modified by inclusion of a presynaptic striatal dopamine dysregulation conceptualized as the final common pathway responsible for the misappraisal of stimuli characteristic of emergent psychosis.[33] In our study, we showed that aberrant activation in this neural circuit (frontal areas and caudate head) is present at ages 14 and 19 years in individuals with a prodromal psychotic phenotype.

Ethologic observations have traditionally distinguished between appetitive (anticipation or reward, motivational phase) and consummatory (outcome/feedback of reward, hedonic response) stages of reward processing involving ventral striatum and ventromedial frontal cortex.[34,35] In our studies, 3 ROIs that resulted from the feedback contrast were located in left and right middle frontal gyri; 1 ROI that resulted from the anticipation contrast was located in dorsal striatum. A recent, small fMRI study from the IMAGEN sample[10] showed increased activation in the right anterior/middle cingulate gyrus and decreased activation in the left fusiform gyrus in the MID in individuals with PLEs. However, the authors of that study used a smaller sample, assessed PLEs at age 14 years, and used a less-extended assessment tool focusing on perceptual abnormalities and delusional thoughts.

The neuropsychological assessment showed that the low PLEs group manifested higher omission errors compared with the high PLEs group at age 14 years, suggestive of reduced inhibitory control, despite the cross-sectional neuroimaging finding of increased frontal brain activation. However, a decrease in AGN scores from ages 14 to 19 years, which corresponds to an improvement in affective/inhibitory control, was observed in both the high and low PLEs groups and was associated with the longitudinal neuroimaging finding of an increase in brain activation at frontal ROIs from ages 14 to 19 years, which was significant only for the high PLEs group. This finding lends support to the proposal that there were no significant differences in explicit cognitive control between the high and low PLEs groups compared with an implicit compensatory cognitive control mechanism that was seen only in the high PLEs group.

Limitations

There are some limitations in our study; we selected high and low decile scorers on CAPE-42 to identify the 2 most polarized groups that would best represent the relative high and low risk for psychosis phenotypes; however, CAPE-42 scores were moderate in our sample. Because our stratification was based on CAPE-42 scores at age 19 years and we did not have available scores at age 14 years or intermediate ages, it was not possible to track the evolution of PLEs between the 2 points. We have viewed the high PLEs phenotype as a proxy for the prodrome for psychosis; however, PLEs can have multiple clinical outcomes, thus leading to a variety of psychopathologic conditions other than psychosis. The lack of transition to psychosis data limits the use of our high PLEs group as a measure for the UHR population. There was a greater representation of the male sex in our low vs high PLEs groups, despite a male preponderance being a common epidemiologic trend in this clinical field.[36]

Conclusions

Adolescents with high levels of PLEs performing a reward processing task demonstrate decreased activation of frontal and limbic areas at age 14 years and a differential increase in right middle frontal activation from ages 14 to 19 years. Given the nonclinical nature of this sample, this finding could represent a compensatory developmental change that permits cognitive control mechanisms to contextualize the PLEs sufficiently to preclude their evolution to clinical intensity. This finding lends support to a 2-stage process in the emergence of psychotic symptoms, with failure of cognitive control as the key event in transition to functionally relevant symptoms. The ongoing follow-up of this sample will permit evaluation of this change as a useful brain biomarker for the psychosis or other broader psychiatric phenotypes.

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